The epidemiology of birthweight and placental weight in New Zealand

Volume 1 (Text)

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Department of Paediatrics

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy,
University of Auckland, July 1997
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Volume 2 (Figures and Tables)

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Abstract

The introduction to this thesis is a literature review. Kramer, in a study commissioned by WHO, reviewed the literature prior to 1985 on low birthweight. This is extended, mainly in respect to infants who are small for gestational age, with emphasis on important findings in relation to birthweight since that time. Work in New Zealand on birthweight is also summarised. The literature is also reviewed in respect to the mechanisms in the pathway between the placenta and the fetus, and in respect to recent work suggesting a link between birthweight and disease in adult life.

This thesis examines factors that influence birthweight and placental weight.

Birthweight for gestational age percentile curves for the New Zealand population were firstly defined. Small for gestational age (SGA) infants could then be categorised.

The thesis considers two sources of data, the first a cross-sectional sample of the New Zealand population from 1987 to 1990 (the control subjects of the New Zealand Cot Death Study, a national case-control study on sudden infant death syndrome), and the second a hospital population in Auckland (National Womens Hospital (1992)).

These two datasets are investigated to determine factors that influence birthweight in a univariate situation and then in the multivariate situation. Independent variables are considered using \textit{a priori} categorisations and where appropriate Quantile-Quantile (Q-Q) derived categorisations determined by producing plots of the quantiles of cases versus controls.

A number of variables under the headings of socio-demographic, lifestyle, genetic, obstetric and nutrition are examined and found to be associated with the outcomes of interest at the univariate level. After controlling in multivariate analyses a number of variables are found to be no longer significant, however some show strong relationships.

The variable relating to smoking in both datasets shows the greatest detrimental effect on the outcomes considered in respect to birthweight. This confirms that in New Zealand, as in other places in the world, smoking has significant consequences on birthweight. The data is also investigated for the timing of insult to the fetus from smoking, and is found to be most important during pregnancy.
Comparison of the results comparing those obtained using a binary outcome for SGA, and those obtained using birthweight continuously, show relatively consistent results. The odds ratios and the decreases in birthweight obtained from both datasets show a relatively linear relationship between the two.

An examination into whether a distinct group of individuals exists in respect to having large placentae for birthweight, indentified an artefact in the dataset relating to recording of placental weight for twins. After removal of twins from the dataset, examination of factors that influence placental weight showed that the factors that influence placental weight are not the same as those that influence birthweight. In particular smoking is found not to influence placental weight, and haemoglobin, which has no influence on birthweight, is found to be inversely associated with placental weight. Other factors such as parity are found to influence placental weight in the same proportion in which birthweight is affected.

In conclusion this thesis shows that factors investigated in New Zealand are consistent with findings in the international literature in relation to birthweight. The results on factors that influence placental weight add to the international literature on a topic on which little work has been carried out.

The results of this thesis point to areas where future research needs to be carried out, in particular in relation to maternal nutrition during pregnancy and maternal energy expenditure during pregnancy. There is also a need for further research into the relationships of factors on placental weight and the ratio of birthweight to placental weight, and how these relationships affect health outcomes in childhood and adult life.
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This thesis is dedicated to the memory of my grandparents, and their fore-bears, without who’s individual struggles through the passage of time the existence of this thesis in this form would not have been possible. It now seems they may have played a greater part in further generations of their families than one would ever have imagined.

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Abbreviations used in this thesis

- e.g. example
- g grams
- i.e. that is
- kcal kilo calories
- lb pounds
- mm millimetres
- s.d. standard deviation
- s.e. standard error
- AGA Appropriate for Gestational Age
- BMI Body Mass Index
- Hb Haemoglobin
- Hg mercury
- Ht Haematocrit
- ICD International Classification of Diseases
- IQR Inter Quartile Range
- IUGR Intra Uterine Growth Retardation
- LBW Low Birth Weight
- LQ Lower Quartile
- MCV Mean Cell Value
- MN Mononuclear
- MSSI Maternal Social Support System
- NWH National Womens Hospital
- NHSS National Health Statistical Services
- NZCDS New Zealand Cot Death Study
- OR Odds Ratio
- PAR Population Attributable Risk
- PMN Polymorphonuclear
- RDS Respiratory Distress Syndrome
- RR Relative Risk
- SAS Statistical Analysis System
- SES Socio Economic Status
- SIDS Sudden Infant Death Syndrome (cot death)
- SGA Small for Gestational Age
UK  United Kingdom
UQ  Upper Quartile
US  United States of America
WHO World Health Organisation
Chapter 1: Introduction

1.0.1 Definitions

Low birthweight (LBW) can result from a short gestation (preterm birth (<37 weeks)), intrauterine growth retardation (IUGR), or a combination of both. Small for gestational age (SGA) is often used synonymously with intrauterine growth retardation, however small for gestational age infants are not necessarily growth retarded. For the purpose of clarity, small for gestational age will be used in this thesis as it makes no judgment on whether the infants have growth retardation or not.

The risk factors of low birthweight, (which is defined as less than 2500g), are difficult to interpret because of confounding from gestation, since some factors may be related purely to preterm birth or to small infants born at term (>37 weeks completed gestation). Furthermore no account is taken of infant sex which is known to be associated with birthweight.

1.0.2 Outcomes

Decreased birthweight due to both preterm and SGA infants, has an important influence on fetal and neonatal mortality, though much of this relates to preterm delivery. Low birthweight infants are known to be at an increased risk of sudden infant death syndrome (SIDS) than their normal birthweight counterparts. The risk of SIDS in New Zealand has been shown to be almost six-fold for infants less than 2500g in comparison to those 3500g or more. More specifically SGA infants are also known to be at an increased risk, with the risk increasing the lower the birthweight percentile of the infant (Thompson, unpublished data).

SGA infants are also known to be at an increased risk of morbidity in early life and continuing problems in later life, such as congenital abnormalities, and cerebral palsy. In childhood, SGA infants have also been shown to have a higher prevalence of poor neuromotor competence, poor language development, be worse in fine and gross motor co-ordination, and be more likely to have behaviour disorders. Along similar lines there are reports of lower educational achievement and learning handicaps among SGA infants. A higher risk of developing asthma has also been reported in SGA infants.

In addition, SGA infants are more likely to have physical and developmental delays. It has also been shown that they are more likely to be left-handed and have mixed undetermined hand, foot and eye dominance.
Although postnatal factors influence growth after birth, the weight of the baby at birth is also thought to have an effect on the growth of the infant. It has been shown that SGA infants are more likely to exhibit growth deficiencies which may be permanent. SGA infants with low ponderal indices have reduced postnatal catchup growth and greater cognitive deficits than those who have normal ponderal indices.

SGA has also been shown to have an effect in adult life. For instance, people with schizophrenia have been shown to have had lower birthweights. Also, recent work has indicated further developmental problems in adult life with smaller infants more likely to develop cardiovascular disease and non-insulin dependent diabetes. Hence factors which affect growth in utero, may continue to have an effect throughout an individuals natural lifetime. This will be discussed in more detail later in this chapter.

1.0.3 Aims

This thesis aims to look at factors that affect birthweight in New Zealand with two aims in mind: Firstly, to determine whether risk factors in New Zealand are the same as in other countries. And secondly, to determine the size of the effects in the New Zealand population associated with these factors.

In the long term, this may well enable birthweight to increase amongst infants in New Zealand by acting to prevent potential risk factors and causal determinants.

An important limitation of earlier New Zealand studies, as will be described below, is that their analyses only controlled for a small number of variables, and the likelihood of residual confounding is high. This thesis will expand the knowledge of the epidemiology of SGA infants in New Zealand by examining data sets with a wide range of variables with multivariate methods to control for confounding. Many of the risk factors analysed in this thesis have not been reported previously for New Zealand infants. Results from this work may well be used as the basis for public health policy in New Zealand based on both the results from the New Zealand data contained herein and results from review of the international literature.
Little work has been done in New Zealand in relation to factors affecting birthweight. Those that have been done are described in detail below. One is from routinely collected birth data, the second from a mostly European hospital population in Dunedin some time ago.

The only study in New Zealand looking at risk factors for low birthweight (LBW) (<2500g) is by Borman et al. who used routinely collected data for all births in New Zealand from 1981 to 1983. The study was carried out because of concern of the increasing rate of LBW in New Zealand at that time, and there was little detailed information on the epidemiology of LBW in New Zealand. The Borman study found a number of associations that will be described in more detail below. These associations however, are in general, uncontrolled for confounders.

Borman found in his study found that female infants had a relative risk of 1.15 (95% C.I.=1.10,1.20) of being LBW compared to male infants. The rates of LBW were 49.70/1000 and 56.96/1000 for males and females respectively. This highlights the point previously made in regard to using SGA as opposed to LBW, since female infants are more likely to be LBW, this will be discussed further in chapter 2 of this thesis.

The rate of LBW was highest amongst Maori (79.38 per 1000 live births), and lowest amongst Pacific Islanders (39.88 per 1000) in comparison to Non-Maori, Non-Pacific Islanders (49.81 per 1000). Consideration of ethnicity of both parents found that the lowest risk occurred when both parents were of Pacific Island origin, but was increased when either parent was of Maori origin, and further increased if both parents were of Maori origin. Also of note was the place of birth for the Pacific Island mothers. If the mother was born in New Zealand then they were at an increased risk of giving birth to an LBW infant, whilst those mothers born in the Pacific Islands were less likely to have a LBW infant. A possible explanation for these findings is the difference in smoking rates reported between ethnic groups with Maori having high rates and Pacific Islanders low rates.

Looking at social class in the Borman study by using a standard New Zealand scale known as the Elley-Irving scale (which is based on income and education), showed that social class found to be was inversely associated with risk of LBW. A test for trend was found to be significant and remained significant after controlling for maternal ethnic origin. Mothers who gave birth exnuptially where at a higher risk of giving birth to a LBW infant than those who gave birth nuptially, RR=1.61 (95%CI=1.54,1.69), and this also remained significant RR=1.48 (95%CI=1.41,1.55) after adjustment for ethnic origin.
The data from the Borman study showed a slightly increased risk for mothers less than 20 years of age, and a non-significant increase for those older than 40 years of age in comparison to those mothers who were between 20 and 24 years of age. In contrast, there were decreases in risk for those 25 to 29 years old and between 30 and 34 years old, compared with mothers aged 20 to 24 years of age. This suggests a U shaped relationship between maternal age and LBW.

In the Borman study a significant decrease in risk was found after adjusting for maternal age, for those mothers having their second through fourth pregnancies, in comparison to those on their first pregnancies (relative risk approximately 0.7). Mothers with greater than three previous pregnancies were at a slightly, but not significantly, decreased risk, in comparison to the primiparous mothers.

The Borman study also showed geographical variation in LBW rates, but only among Maori (the risk was lower in the South Island than in the North Island, RR=0.64, 95%CI=0.51,0.82). In contrast there was little difference in Non-Maori LBW rates between the two islands. Little difference was found in rates of LBW by season.

Another study in Dunedin, looked at the effect of maternal height on singleton births of European descent in New Zealand. This study found decreases in head circumference, crown-heel length, and birthweight associated with decreasing maternal height. The decreases detected in all measurements were smaller in female infants than male infants. For birthweight they were 25g and 85g for each 5cm decrease in maternal height respectively. Adjusting birthweight for maternal height was found to decrease the incidence of an SGA infant among small mothers and increase the incidence among tall mothers.42

1.2 International Literature

Low birthweight in general has been studied extensively throughout the world. Comparison of such work has been difficult due to different definitions of the particular outcome of interest in the various studies. These studies also tend to combine both term and preterm births within the definition of LBW, thereby making it difficult to determine whether effects due to a particular factor are related to only gestation, SGA or a combination of both.
Where possible the literature used in this thesis will focus on SGA and LBW amongst term infants. Other studies which include preterm infants are included where it is felt that the results add to the importance of a factor and its relation to LBW.

The studies considered in this chapter are selected from the extensive number of publications on the following grounds: 1. The study had to be well enough described that the population that had been studied could be identified, along with the sample size and the method by which the data was collected. 2. That the confounding variables the authors had controlled for in estimating the effect of a particular variable on the chosen outcome were described.

Some of the studies reviewed here are purely descriptive, meaning that the data is routinely collected so that control for other important factors (such as smoking) is not possible. However, such studies enable the New Zealand situation to be considered as a whole in relation to other countries. Other studies tend to be either extensive in their design (i.e. looking at and controlling for large numbers of variables) or looking in depth at the relationship of a specific factor to the outcome.

Variables in this literature review for which there are large amounts of information have corresponding tables which are given in Volume II: Figures and Tables. The tables provide the reference number, the country where the study was carried out, whether the study used routinely collected data, was retrospective or was prospective. They also include the confounders that were controlled for and any comments about the study, along with the outcome considered, and the strength of the association of the variable with the outcome, in each particular study.

In order to give the literature review structure it has been split into several sections based on the taxonomy of Kramer, which is described below. This, in general, groups related variables together, and also defines groups of variables that will be considered together for analysis later in this thesis. The sections that the review is broken into are; socio-demographic, maternal lifestyle, genetic, obstetric and nutritional factors.

In order to provide a starting point from which to work it was decided to use a summary of literature that had already been written. This had the advantage of not having to review literature that was no longer current. Furthermore it would have been pointless to review literature that had already been reviewed. This review is described below.
In 1985, Michael Kramer was commissioned by the World Health Organisation (WHO) to summarise the work on various factors associated with gestational age, prematurity, birthweight and intrauterine growth retardation (IUGR). The term intrauterine growth retardation is used in Kramer's review as a synonymous term for small for gestational age. His literature review considered studies from both developed and undeveloped countries and, where possible, summarised the size of the effects of variables using only those studies which met acceptable criteria for control of confounding and study design. The factors that he considered essential to control for, when looking for a direct effect on birthweight of a given variable, will be described in the introduction to each variable and in the corresponding tables. To be included in his analyses, studies were classified as having satisfactorily or partially met certain standards. These standards, which differ depending on the factor in question, included: definition of the target population and study sample, description of study participation and follow-up rates, demonstration of the appropriate time sequence between factor and outcome, use of an experimental design, and control of potential confounders. For a study to be considered as satisfactorily having met the standards, it must have fulfilled the majority of his pre-determined criteria, though perfect conformity was not required, whilst to be included for analysis by partially meeting the criteria, a study must have given attention to rigorous design and analysis but fulfilled less than half of his pre-determined criteria.

Since Kramer's review in 1985, extensive work in this area has continued, though the standard of study and definitions of outcome have generally not improved. This literature review attempts to set the scene for the work contained in this thesis by starting with the standpoint of the Kramer summary and extending it with the literature published through to September 1994, as indexed by Medline.

1.2.1 Socio-Demographic Factors

Socio-demographic variables play an important role in determining birthweight. Although unlikely to have any direct relationships to birthweight they generally provide a good guide to the social circumstances of the mother. Variables in this category tend to be related to each other, and the extent to which they are associated varies within populations and possibly even within outcomes. As such, it is usually seen as being appropriate to measure a number of such variables in order to allow good measurement of social circumstances.

The variables considered below from the literature review are: 1) socio-economic status, 2) maternal education, and 3) marital status.
1.2.1.1 Socio-Economic Status

Socio-economic status in the international literature is often measured by classifying individuals into predefined socio-economic groups based on maternal and/or paternal occupations, although sometimes family income is used.

Kramer's literature review points to the differences in socio-economic status between developed and developing countries. In developed countries, low socio-economic status groups are more likely to contain women who belong to ethnic minorities, are smokers, and belong in other risk categories; Whereas in developing countries, women are more likely to be smaller and have poorer nutrient intakes. He also suggests that any analysis looking for a direct effect of socio-economic status should control for ethnicity, along with, when possible; height, weight, age, weight gain or caloric intake, genital tract infections, smoking, alcohol, and antenatal care. Kramer points to the fact that any association with socio-economic status is likely to be indirect, although long term improvement of social conditions is likely to lead to improved public health in many areas.120

Studies considering income as a measure of social class have found differing results. Two studies from the United States reported that those with the lowest incomes had the highest rates of LBW.44,151 A further study however has shown a curvilinear relationship between median family income and LBW,92 although a further study in Canada found no relationship.19 Meanwhile in the United Kingdom (UK), Brooke et al found that manual social class had an effect on LBW, but income was not related,41 whilst Stein et al found that low income was a better predictor of LBW than unemployment or working class.222

In Scotland, routinely collected data has shown increased risks for those in the low social classes, and a decreased risk for those in the high social classes, in comparison to those of middle class standing. The risk was almost identical for both primiparous and multiparous women.187 Similarly a further study found increased rates of LBW in families where the mother or father had manual jobs, with the risk being further increased if both parents worked in manual jobs.66 A study in Spain which used four broad categories of profession instead of a manual/non-manual classification also showed increased risks of SGA amongst those in the lower profession categories.169 Virji & Talbot however found no differences in socio-economic status after controlling for confounders, including smoking and alcohol use, between white and blue collar workers.235
A further definition of social class by Bell & Lumley in Australia, using postal codes, also found that those in the lowest socio-economic deciles had an increased LBW risk in comparison to those in the highest decile.\textsuperscript{34}

In all, the cumulative evidence, a summary of which is presented in Table 1.1, points to an increased risk amongst women in the lowest socio-economic groups. However, the increased risks in these groups are relatively small or disappear after controlling for confounding variables, especially age, parity and smoking.

1.2.1.2 Maternal Education

Maternal education is often considered as a measure of socio-economic status, though it is also often considered independently in many analyses. Of the social indicators it is also the one that is likely to be the most modifiable in the short term.\textsuperscript{120} Variables that should be controlled for are the same as those for socio-economic status.

Studies in the United States show a decreasing rate of LBW with increasing maternal education.\textsuperscript{60,117} Furthermore one of these studies showed a decreasing rate of LBW over time as maternal educational levels improved, though no confounders were controlled for. From 1973 to 1983, LBW rates fell from 46.4 to 39.2/1000 live births in whites and from 101.6 to 95.7/1000 live births in blacks, while the percentage of mothers attaining less than year 12 at school dropped from 26 to 19 percent in whites and 49 to 35 percent in blacks.\textsuperscript{117}

A study in the Netherlands has also shown an increased risk amongst those with low educational levels in comparison to those of high education, with a decreased mean birthweight of 6.7% at the univariate level. This reduced to 4.0% (95% CI=0.7,7.4) after controlling for a number of confounders including smoking.\textsuperscript{230}

Furthermore a study in Canada found an increased LBW risk amongst mothers reaching only 12 or 13 years education OR=3.08 (95%CI=1.47,6.43) or less than 12 years education OR=2.21 (95%CI=1.12,4.37) compared to those having more than 13 years education. However, no relationship between maternal education and infant size was found after controlling for maternal height and weight.\textsuperscript{19}

The effects of maternal (and paternal) education are likely to be related to those of social class, and care needs to taken when interpreting the effects of such a factor in relation to possible confounders. Educational levels play an important part in the pathway to occupational status and hence socio-economic status, amongst
other variables. However educational status should not be overlooked as the factor most amenable to change in the short term, and the lead on benefits from its improvement to other social variables.

1.2.1.3 Marital Status

In the past marital status has tended to be used as an indicator of socio-economic status, under the assumption that married women were generally of higher socio-economic status than single women. In today's environment however these assumptions are not necessarily true due to the fact that many more parents are sharing economic resources without being married. Marital status is now more a variable that reflects personal choice and lifestyle. Kramer is his literature review found that the effect of marital status on IUGR was inconclusive. 120

Another problem is that most studies that focus on marital status as a risk factor tend to involve the use of routinely collected data, and hence do not have the ability to control for potential confounders (such as smoking). Kramer suggested that the following variables be controlled for when possible: height, weight, age, birth interval, gestational weight gain or caloric intake, genital tract infection, smoking, alcohol, and antenatal care. He also stated that it was essential to control for ethnicity and socio-economic-status. 120

Studies using routinely collected data have shown consistent results. In Scotland, studies showed an increased risk of LBW187,200 and SGA186,187 amongst single mothers compared to married mothers, and one of these studies showed that this effect occurred in both primiparous and multiparous single mothers. 187 Similarly, in the United States, an increased rate of LBW was found among unmarried mothers compared to married mothers. 117 Another study, however, showed that both single and previously married mothers had equally higher risks of SGA or LBW infants than currently married mothers. 200

Studies able to control for confounders beyond those that are routinely collected have shown varied results. Most have shown effects of marital status at the univariate level, which have continued after controlling for confounders, 16,82,133 however these studies did not control for smoking. The only study to control for smoking found no association between marital status and LBW.8

Other studies have also shown contrasting results in different ethnic groups, suggesting cultural differences in marriage. 217 Other studies have found no effect whatsoever, however marital status was significantly related to a number of other confounders, such as age, education and social class. 140
In summary, the effect of marital status is confounded by both socio-economic and other variables, which makes comparisons of studies difficult (Table 1.2). The effects associated with marital status in multivariate analyses in general have been relatively small, and hence, are not likely to be of huge importance, however marital status remains an important confounder. Furthermore, simply issuing marriage certificates to couples is not going to change the risk of small infants amongst this at risk group. One unresolved issue is how women previously married or living in de facto relationships should be categorised for marital status. The effects of both groups is not consistent across studies and this may in part be due to issues of values amongst different ethnic groups and populations.

1.2.2 Maternal Lifestyle Factors

Maternal lifestyle factors reflect the way in which the mother of the infant chooses to live. A number of these variables within this category of maternal lifestyle factors may well have direct relationships to the outcome of interest. The variables considered under this heading will be; 1) tobacco smoking, 2) marijuana usage, 3) narcotic and other drug use, 4) caffeine consumption, and 5) alcohol consumption.

1.2.2.1 Tobacco Smoking

Smoking is commonly known to be the most important variable in relation to birthweight. Kramer’s literature review points to smoking as the most thoroughly studied factor in relation to pregnancy outcomes and suggests studies looking at smoking should control for maternal ethnicity, weight, age, stress and alcohol consumption. In his study, Kramer found a sample size weighted birthweight deficit for infants of smoking mothers to be 149.4g compared to infants of non-smoking mothers, with the per cigarette decrease in weight being 11.1g per cigarette per day. A sample size weighted estimate of the relative risk of an IUGR infant was 2.42. At the time of Kramer’s review, whilst smoking was accepted as the most important risk factor for IUGR, there was still debate on the effects of stopping smoking during pregnancy and the effects of passive smoking, for instance, from other household members or in the workplace.120

Studies consistently show increased risks of SGA amongst smokers in comparison to non-smokers,75,240 though some report differences in the effects of smoking amongst different ethnic groups.183 A large number of studies not only show increased risks amongst smokers, but also an increased risk in relation to the number of cigarettes smoked.23,41,128,171,175,179 One study has reported that these dose-relationships are independent of
age and parity. In contrast, another study reported a non-significant increase in risk for those who smoked smaller amounts of tobacco (1-10 per day).

Some studies considering dose have not just looked at the number of cigarettes smoked, but also the yield of tar, nicotine, and carbon monoxide of the cigarettes. Peacock et al found that smokers of small amounts of low yield cigarettes were at no increased risk of having a small infant than those who did not smoke. They also found that those mothers who smoked large numbers of low yield cigarettes, or small numbers of high yield cigarettes, had a similar decrease in birthweight and that a threshold effect existed at 13 cigs/day or 15 mg/cigs carbon dioxide. In support, Olsen et al also reported incremental decreases in birthweight with increasing nicotine content of cigarettes.

A number of studies have now examined the effects on birthweight of mothers who gave up smoking during pregnancy. These studies have shown slightly divergent results but do point to a general trend. Two studies showed no difference in birthweight of infants of mothers that gave up smoking prior to or during pregnancy, in comparison to infants of non-smoking women. Another study showed no difference in those who gave up before or in early pregnancy. Frank et al however found a small decrease in birthweights amongst mothers who quit after conception, whilst Mainous reported a small increase in risk of SGA for those who quit in the first trimester, while those who did not give up until after the first trimester also had much increased risks.

Studies which considered passive smoking have also reported differing results. Ogawa found no effects of passive smoking where the mothers were non-smokers. Similarly, Ahlborg & Bodin found no effect of passive smoking in either the home or the workplace. On the other hand Mathai et al found decreased birthweights where the mother lived with a smoker, and Fortier reported passive smoking to have effects similar to those of mothers that smoked 1-5 cigarettes per day. Zhang & Ratcliffe found confusing results with infants having lower birthweights if the father smoked <20 per day, but a heavier infant if the father smoked 20 or more per day.

Using another approach of looking at the trends of birthweight and smoking over time, Meyer et al found that even though the proportion of SGA infants had decreased over time (1971-73 to 1983-85) from 11.1% to 9.1%, the percentage of women smoking and the amount smoked had increased from 9.3% to 22.2% during the same time period. The average number of cigarettes smoked per day also increased during this time from 6.7 per day to 10 per day. This has serious implications for smoking as a risk factor around the world, which is likely to become even more important with the passage of time.
A table summarising the results from all these areas is presented in Table 1.3.

In conclusion, there is no doubt that smoking remains the most important risk factor for SGA in the developed world. The evidence points to a clear indication of increasing risks with increasing amounts smoked though it is also becoming clear that yield of nicotine is also important. Women who give up smoking prior to or in early pregnancy, reduce their risk of giving birth to a smaller infant, though non-smoking both before and during pregnancy must remain the safest public health option. Effects of passive smoking are still unclear (possibly due to the difficulty in measuring exposure), and further research needs to be carried out in this area.

1.2.2.2 Marijuana Usage

Marijuana use is quite common. A study in the US found 4.1% of women reported occasional marijuana use and 5.4% of women reported using marijuana 2-3 times a month.\textsuperscript{100} While in Australia 5.4% admitted marijuana use and 0.5% more than once a week.\textsuperscript{86} When studying the effects of marijuana on birthweight it is essential to control for smoking and alcohol consumption. Other likely confounders that should be controlled for are ethnicity, weight, age, socio-economic status and stress. The questioning of subjects on the use of illicit substances is one which can of course bring recall bias into question. Differential bias however seems unlikely as there is no reason why cases and controls should be any different in reporting the use of illicit substances. Such studies also usually guarantee the confidentiality of information given by the respondents. For example in the New Zealand Cot Death Study (NZCDS), where subjects had the opportunity not to answer, none of 451 SIDS parents and 2 of 1586 control parents refused to answer the question relating to marijuana use.

Kramer in his review reported no effect of marijuana use on either gestational age adjusted birthweight or IUGR.\textsuperscript{120}

Hatch et al reported mean birthweights of 3393g amongst non-users of marijuana, 3327g amongst occasional users of marijuana, and 3206g for regular users of marijuana. They also reported differences in SGA, the percentages being 5.2%, 7.2% and 9.1%, respectively, for the above groups. When whites and non-whites were considered separately, an effect was seen only in whites. Controlling for gestation, parity and smoking, however, rendered these effects non-significant among occasional users. Regular users, however, continued to show increased risks of an SGA infant OR=2.3 (95%CI=1.3,4.1).\textsuperscript{100} Other variables such as alcohol, caffeine, age and education were removed from the model due to their non-significance. When birthweight

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was considered continuously, and smoking and caffeine amongst other confounders were controlled for, none of the above categories showed significant differences in mean birthweights. Looking just at whites, there were decreases of 24g and 97g amongst the occasional and regular users respectively (p=0.07). Similarly Gibson found a suggestion of an effect at the univariate level (p=0.10). After controlling for parity, age, alcohol and tobacco use the significance reduced slightly (p=0.12).

It seems any effect from marijuana is mediated by confounding with other maternal lifestyle factors especially smoking, and alcohol usage. Further work is clearly needed to determine if there is any additional effect of marijuana (though indications are that it is relatively small) on top of these other factors and if there are any interactions that may be present between these factors.

### 1.2.2.3 Narcotics and Other Drugs

The general conclusion by Kramer in his literature review of studies that examined narcotics use, was that mothers exposed to such substances gave birth to lighter infants. However, none of the studies reviewed satisfactorily met Kramer’s criteria for analysis, which similar to marijuana use, included controlling for ethnicity, weight, age, socio-economic status, stress, parity, and, in particular smoking and alcohol.

A subsequent study comparing drug users to non-users reported SGA prevalence's of 8.7%, 8.3%, and 2.2% amongst cocaine, other narcotics, and controls respectively. Other studies have found large decreases in mean birthweights (range of 350-700g) for infants of mothers using drugs. As with the studies in Kramer’s review, none of these later studies had controlled for confounders.

Although no good controlled studies have been done in relation to narcotic use, the size of the decreases in birthweight at the univariate level suggest that use of narcotic substances has large detrimental effects on the size of the infant at birth. The type of narcotic seems, from the evidence, to be of little importance, all examined showing detrimental effects of similar sizes.

### 1.2.2.4 Caffeine Consumption

The international literature usually classifies caffeine consumption into the following categories; non-users, light users (1-150mg/day), moderate users (151-300mg/day), and heavy users(>300mg/day) users.
Kramer’s literature review showed almost unanimous evidence that neither caffeine nor coffee consumption by mothers had any effect on birthweight or IUGR. The intake of caffeine is associated with alcohol consumption and smoking and therefore, he points out, it is essential to control for these two variables. Other variables that are appropriate to control for are ethnicity, socio-economic status, weight, age and stress.

Shiono and Klebanoff, in an editorial on the effects of caffeine, similarly concluded that, although many studies were flawed, there was either no risk or the risk from caffeine was so small that only large studies would be able to detect it. Another possibility is that caffeine is only a risk factor in a subgroup of the population, for example smokers.

Since these reviews, studies have shown that mothers with heavy caffeine consumption have increased risks of giving birth to LBW or SGA infants and give birth to infants with lower birthweights. However some studies have shown these increased risks not to be significant at the multivariate level, with one reporting no effect even at the univariate level. Most studies have also concluded that there is no increased risk for infants of light and moderate users over non-users. One study however reported a slight risk of a LBW infant for the moderate users, but no difference in birthweights compared to non-users. Heavy consumers who reduced their consumption have also been shown to reduce the risk of their infants having decreased birthweights compared to those who continue heavy caffeine consumption.

Smoking is the most important confounder for the effect of caffeine consumption in relation to birthweight. Peacock et al found decreased birthweights in both light and heavy smokers with increasing caffeine consumption compared to non-smokers. Fortier et al also reported increasing risks of LBW with increasing caffeine consumption within smoking categories. Similarly Olsen et al found decreases in birthweight with increasing coffee and tea consumption, especially among smokers, which they suggested may be due to a difference in the metabolism of caffeine caused by smoking.

Larroque et al, however, have reported that there is no clear relationship between caffeine consumption and birthweight within different groups of tobacco use.

In summary, any effect of caffeine consumption on SGA is only in the heaviest category of caffeine consumption and, even then, the effect is only of moderate size. The effects of caffeine consumption on SGA are confounded significantly by smoking. Table 1.4 shows the size of the effects of the studies reported above.
1.2.2.5 Alcohol Consumption

Kramer's literature review found that a majority of studies analysing the effect of alcohol consumption on SGA reported significantly lower birthweights for mothers who consumed higher doses of alcohol during pregnancy, (a sample-size weighted estimate was found to be 155g associated with 2 or more drinks per day) compared to non-drinkers. Again it is essential to control for smoking when looking for an effect on SGA due to alcohol and, similarly, it is appropriate to control, if possible, for ethnicity, weight, age, socio-economic status and stress. The studies reviewed by Kramer also indicated that alcohol intake later in pregnancy may be a more important determinant of birthweight. A totally safe amount of alcohol during pregnancy is not known. Most studies however have not detected effects on birthweight or IUGR from low amounts of alcohol. A more recent report on alcohol by Larroque also came to the same conclusions.

In general, alcohol consumption decreases in pregnancy. For example Day et al reported that the number of heavy users dropped from 36.6% to 13.6% from the first to third months of pregnancy while non-users increased from 31.1% to 49.1%. Alcohol consumption continued to decrease through the second and third trimesters. In Australia, Gibson et al found 25.5% of pregnant women abstained from alcohol consumption and 67.9% reported one or less alcoholic drink per day.

A number of studies have found no significant effect of alcohol consumption during pregnancy on birthweight or rates of either LBW or SGA. Other studies have shown an effect on birthweight from alcohol which, like that of caffeine, appeared to be solely among the heavier consumers, although significant trends with increasing alcohol consumption have also been shown.

Again as with caffeine consumption, the effects of maternal alcohol are confounded by smoking, and the results reported have been inconsistent in their findings. Little et al reported decreasing birthweights with increasing amount of alcohol amongst a population of non-smoking mothers. Larroque et al have also reported no effect of alcohol on infants of moderate smokers, however alcohol consumption still had an overall effect after controlling for confounders. Conversely though, Brooke et al have reported no effect on birthweight of alcohol amongst non-smokers, but a strong effect of alcohol was seen amongst smokers, which was consistent amongst both light and heavy smokers.
In other alcohol related studies, Tolo & Little found no increased risk of a LBW infant to mothers who binged in the first two trimesters of pregnancy compared to those that did not,\textsuperscript{227} whilst Savitz et al found no effect of paternal alcohol consumption on infant size.\textsuperscript{202}

Studies reporting the effects of alcohol on birthweight are not consistent (see Table 1.5) and continue to report conflicting results amongst smokers and non-smokers. A safe amount of maternal alcohol consumption during pregnancy is still unknown, though, in general, detrimental effects of alcohol have been reported only amongst women who are heavy drinkers during pregnancy.

1.2.3 Genetic Factors

Genetic factors are determined by the specific genetic disposition of the mother which, in most cases, she has no control over. Variables included in this section are: 1) infant sex 2) ethnicity, 3) maternal height, 4) maternal pre-pregnancy weight, and 5) maternal body mass index; although it is acknowledged that these factors are also associated with maternal lifestyle.

1.2.3.1 Infant Sex

It has long been reported that female infants are lighter than male infants, with differences in weights being reported as early as 1943 by Anderson et al.\textsuperscript{18} In Kramer’s 1987 literature review\textsuperscript{120} all but 2 of 66 studies showed that the sex of the infant had no effect on the gestational age of the fetus. A weighted analysis of the studies identified males as 126.4g heavier in developed countries and 93.1g heavier in developing countries. A meta-analysis of the studies that estimated the relative risk for IUGR (equivalent to SGA since gestational age does not appear to differ), found female infants had a relative risk of 1.19 for SGA compared to male infants.

In 1989, Goldenberg et al.\textsuperscript{200} summarised published percentiles since 1963 showing that male birthweights are generally higher than those of females. He stated:

"Since there do not appear to be more risk factors in mothers who are delivered of male infants and since female infants do not appear to be at a disadvantage because of their lower weight, it seems reasonable to use sex-specific standards. Otherwise infants classified as having IUGR will include a disproportionate number of apparently healthy female infants."
A more recent study by Copper et al has shown that after controlling for several potential genetic confounders, female infants were 159g lighter than males. They also found that female infants were in fact smaller or the same in all length and circumference measurements.63

In summary there is little doubt that male infants are heavier than female infants and hence gender needs to be taken into account when defining groups that are at risk due to their size.

1.2.3.2 Ethnicity

Differences in mean birthweights have been reported in different ethnic groups and may be due to a genuine genetic effect or due to differences between ethnic groups in the prevalence of other risk factors that are associated with birthweight. Furthermore, effects of ethnic origin may also be due to cultural differences. For the purpose of this work, ethnicity will be considered as a variable that may have a genetic effect, although it is recognised that any effects on birthweight may not in fact be due to genetic components of the variable.

Kramer’s review suggested that factors associated with ethnicity probably include maternal age, parity, inter-pregnancy interval, work in pregnancy, genital tract infection, smoking, alcohol, and antenatal care. He also points out the need to control for maternal height and weight, socio-economic status, and weight gain or caloric intake when making ethnic comparisons.120 The review also suggested that, while there was no effect of ethnic origin on gestational age, it was likely that there was an effect on birthweight.

The majority of studies looking at ethnicity and its effects on birthweight have come from the United States and have compared Black and White ethnic groups. These studies have shown that Black infants are significantly smaller than White infants, or that Blacks have higher rates of LBW than Whites.50,111,117,134,155,165,168,240 Blacks having been consistently shown to have approximately a two-fold increased risk, as can be seen in the upper part of Table 1.6 where rates and ratios of Blacks to Whites are shown. Wen et al, after controlling for a number of confounders including social class, parity, smoking, alcohol and constitutional factors, still found an increased LBW risk amongst blacks compared to whites.240

The differences between Blacks and Whites seem to be less divergent in the lowest socio-economic classes than among the more affluent social groups.60,220 Some studies have suggested that confounding factors between Blacks and Whites may vary with social class155,183,240 although most of these studies were not consistent in the direction of the confounding. A study by Kallan has suggested that a number of variables
along the causal pathway differ between races including marital status, prior LBW, planned pregnancy, and smoking.110

A countrywide study in the United States looked at infants from mixed marriages found that the risk of a LBW infant increased from the White/White combination to White mother/Black father to Black mother/White father, with the highest risk for Black/Black. While the ethnic group of the mother had more effect, the effect of the father’s ethnic group was still significant.154 Another study, based only on residents living in the city of Chicago, found a decrease in risk of a Black mother/White father but no difference between White mothers/Black fathers in comparison to both parents being White.61

In addition, some studies in the United States have also shown an increased LBW risk among Asian ethnic groups,8,237 but no differences between Whites and Hispanics.8 The study by Wang et al, though, found that infants delivered by foreign born Chinese and Japanese mothers were heavier than those of US born Chinese and Japanese mothers (they suggest this may be associated with a changing US immigration policy).237

In Israel, Jews and non-Jews have been shown to have similar rates of LBW, and similar mean birthweights, though Jews born outside Israel tended to be heavier with the exception of those born in Asia.164 In the United Kingdom, West Indian and Indian subcontinent mothers were shown to have lighter birthweight infants than Europeans. It was suggested that African and Middle Eastern women in the United Kingdom also had smaller infants, while those of Far East women were larger.246

A study in Australia amongst aboriginal women compared infants who had a known non-aboriginal ancestor to those who did not. They found that males without a known non-Aboriginal ancestor were significantly lighter than those with. There were no significant differences found in the female infants.203

Various places in the world have shown differences in birthweight between ethnic groups living within their communities. Whether these effects are due to genetic differences or are due to maternal size and other risk factors (such as smoking, SES and maternal education), remains unclear. A summary of the results is shown in Table 1.6. Hence with the given evidence one cannot exclude the possibility that there is some genetic component.
1.2.3.3 Maternal Height

Maternal height is in part a genetic factor which influences the height a child will reach at maturity. It is therefore a factor that may influence measurements at birth, including birthweight. Therefore maternal height will be considered as a genetic variable for the purpose of the analyses in this thesis. This fact is emphasised further by Kramer where he states in his review that:

"Maternal height is influenced by genetic potential, skeletal maturity and environmental factors during skeletal immaturity. It can affect intrauterine growth either genetically or by environmental mechanisms, hence imposing limitations on the growth of uterus, placenta and fetus, but probably not gestation."^{20}

Kramer’s review^{120} found that there was no effect of maternal height on gestational age. Based on the studies that controlled for important confounding variables, the most essential of which is maternal weight, there was a 7.8g increase in birthweight for every centimetre increase of maternal height. Other variables that should be controlled for are; ethnicity, age, socio-economic status, parity, birth interval and gestational weight gain or caloric intake. A small number of studies reviewed by Kramer also found an inverse relationship between maternal height and risk of IUGR. Calculations of aetiological fractions suggest that, where populations have large proportions of short mothers, they may account for a reasonable proportion of IUGR infants.

Using routinely collected data from Scotland, Pickering & Forbes^{187} found an increased risk of an SGA infant for shorter mothers (<150cm) of 2.17 and a similar magnitude decrease in risk of 0.5 for infants of taller (≥165cm) mothers, compared with mothers of average height (151cm-164cm). Another study by Pickering^{186} (also using routinely collected information), found similar risks to those reported above in both nulliparous and multiparous mothers.

A study in Aberdeen by Campbell et al standardised birthweight for gestation, sex, parity and maternal size. Standardised birthweight scores were found to increase steadily in 2cm height groups, the increases being equivalent to a 15g change in birthweight per centimetre of maternal height.^{48} Similar work by Wilcox et al (which controlled additionally for ethnicity) found a change equivalent to 8g per centimetre of maternal height.^{247} Similarly Gardosi et al^{83} after controlling for the same factors as above, and maternal weight at first antenatal visit, found decreases in weight from the population mean in 10cm groups for women ≤160cm and increases for those >160cm. The results showed women of shorter stature had babies whose weight
difference from the mean was greater in magnitude than the increase for the taller mothers.\textsuperscript{83} This result has also been reported by Ounsted et al who found in their study that mothers of SGA infants were shorter than the mean height of mothers that gave birth to AGA infants.\textsuperscript{175}

Another study by Kramer et al \textsuperscript{122} found maternal height was significantly related to an increase in birthweight, an increase of 1.6\% of the mean birthweight for gestational age for every 10cm increase in height. This equated to an increased risk of an SGA infant of 1.29 for each 10cm decrease in height.

A international meeting sponsored in part by the World Health Organisation (WHO), looking at maternal anthropometry for prediction of pregnancy outcomes in developing countries, considered maternal height not to have an independent effect on infant birthweight and, instead, viewed maternal height simply as a reflection of total body mass.\textsuperscript{123}

On the other hand, a study in France looking at trends in the rates of SGA infants between 1971 and 1985 found a 20\% decrease in births below the 10th percentile for gestational age over this time period. An analysis to determine the trend in distribution of factors associated with SGA found that during this time period there was a significant decrease in the proportion of women giving birth that were <= 160cm of height from 46.3\% to 42.5\%.\textsuperscript{153}

In conclusion, studies which controlled for confounders have found increasing risks of having a smaller infant with decreasing maternal height. A summary of the results from the studies described is shown in Table 1.7. The benefits of being taller than average do not seem to be of the same magnitude as the increased SGA risks seen in shorter women. Maternal height is of course confounded by such variables as pre-pregnancy weight and body mass index.

1.2.3.4 Maternal Pre-pregnancy Weight

Maternal weight is likely, at least in part, to be due to genetic potential and to affect the weight of the maturing fetus. Maternal weight is also determined however by lifestyle factors such as diet and maternal physical activity. Therefore, for analysis in this thesis, maternal weight will be considered along with the other potential genetic variables.

The studies that Kramer reviewed showed an increase of 9.5g of birthweight for every kilogram increase of maternal pre-pregnancy weight. Because height and weight are associated with each other, height must be
controlled for in the analysis of weight along with, where possible; ethnicity, age, socio-economic status, weight gain or caloric intake, and smoking. Only one study estimated the relative risk of low maternal pre-pregnancy weight on IUGR; this showed an odds ratio of 1.84 for mothers with a pre-pregnancy weight of <49.5 kg compared to heavier mothers.120

The studies by Campbell et al48 and Wilcox et al247 which standardised birthweight for sex, gestation and parity, and, in the latter ethnicity, 247 also adjusted for maternal weight. Campbell et al found an effect of antenatal booking weight, after also adjusting for gestation of antenatal booking, equivalent to 8g per kilogram of maternal weight independent of the mother’s height. Wilcox et al found an effect due to maternal weight but also included a squared and cubic term for weight in the model. Despite this, the magnitudes of the effects seem to be similar.

A study conducted in the North-East of Brazil by Ferraz et al,75 after showing a correlation between pre-pregnancy weight and post-partum weight of 0.79, found a univariate odds ratio for term LBW mothers of less than 50 kg post-partum weight of 2.7, compared to mothers 50kg or more. This decreased to 2.1 (95%CI=1.6,2.7) after controlling for a number of confounders including maternal height and age. Another analysis of this data restricted to multiparous women found comparable risks.76 Nieto et al, conducting a study, in Spain also found increased SGA risks for those <=50kg though the risks they found were larger than those generally reported, possibly because height was not placed in the multivariate model since it was not significant at the univariate level.169 In a similar approach, Dawes & Grudzinskas64 found that low maternal antenatal booking weight (<51kg) was the most effective maternal weight measurement for antenatal detection of SGA infants.

A paper by Gardosi et al83 found that, in comparison to the population mean birthweight, when maternal weight was divided into 10kg categories, mothers in the categories below 61kg had babies of lower birthweight and mothers in the categories above 61kg had slightly heavier babies. Like maternal height, the increase in birthweight of infants of heavier mothers was not as large as the decrease in weight of the infants of lighter mothers. Maternal weight at the first antenatal clinic appointment has also been found to have the strongest correlation with birthweight of all physiological measurements.83

Wen et al’s study, after controlling for a number of factors including height and weight gain, found an increasing SGA risk with decreasing maternal pre-pregnancy weight, although a test for trend was not carried out.240
The report from a WHO sponsored international meeting\textsuperscript{123} concluded that while pre-pregnancy weight and weight gain in pregnancy are related, pre-pregnancy weight is independently related to birthweight.

A table summarising the strength of the effects described above is shown in Table 1.8. There seems little doubt that maternal weight plays some role in the weight of the developing fetus. It may be acting as a surrogate for maternal nutritional sources which are likely to play a role in the initial development of the fetus. Like maternal height, the increased SGA/LBW risks for infants of lighter mothers is of greater magnitude than the decrease in risk for those of heavier mothers, hence indicating the importance of an adequate nutritional state prior to pregnancy.

1.2.3.5 Maternal Body Mass Index (BMI) and weight for height

Maternal Body Mass Index (BMI) and weight for height are highly correlated by definition. Weight for height is defined as a percentage of a reference weight for a given height. Body mass index (BMI) is defined as weight(kg)/height(m)$^2$, also known as the Quetelet index. BMI is often used for monitoring weight gain in pregnancy.\textsuperscript{123}

Abrams and Newman\textsuperscript{8} have shown an increased risk OR=2.36 (95\%CI=1.67,3.33) of SGA associated with infants of those mothers who were pregravid underweight for height, defined as less than 90\% of their ideal weight. The increased risk reported was analogous with other studies. However they found no significant effect of being overweight.

Similarly, Dawes & Grudzinskas\textsuperscript{64} found maternal BMI to be a useful screening test to determine women at risk of having an SGA infant along with low antenatal booking weight and low average weekly weight gain. Similarly, al Eissa et al found low maternal BMI to be one of the most important predictors of LBW in Saudi Arabia.\textsuperscript{13}

A report authored by Krasovec & Anderson, from a WHO sponsored meeting,\textsuperscript{123} noted that weight for height may be a useful tool for monitoring non-pregnant women so that intervention may take place before pregnancy in "underweight" women. However it is more difficult to use during pregnancy as it requires accurate knowledge of the gestational age of the baby. This point seems to be theoretical due to the fact that a large proportion of high risk pregnancies are likely to be unplanned.
1.2.4 Obstetric Factors

Obstetric factors cover a large range of variables. There are a number of variables of interest that are associated directly with the pregnancy including: 1) maternal age, 2) maternal hypertension 3) maternal psychological factors, 4) sexual activity, 5) genital tract infections, 6) urinary tract infections, 7) ante-natal care, 8) ante-partum haemorrhages, and to some extent 9) inter-pregnancy interval. A number of factors relate to obstetric history, which may well have an influencing role in the outcome of the pregnancy in question. These variables include 10) parity, 11) previous small or preterm infants, 12) previous spontaneous abortion, 13) previous induced abortions, 14) previous neonatal death or stillbirths, and 15) prior infertility and in-vitro fertilisation. Each of these will be discussed in detail below.

1.2.4.1 Maternal age

Adolescent mothers and those over 35 years of age at the time of giving birth tend to give birth to infants with lower birthweight compared to mothers in their twenties and early thirties. However, it is considered that age itself is not likely to be directly related to birthweight. Maternal age is related to a large number of other variables. Kramer recommended controlling for ethnicity, weight, height, parity, weight gain or caloric intake, smoking, alcohol and antenatal care when analysing the association between maternal age and birthweight. The youngest and oldest mothers are often found to be in the high risk categories for such variables. Kramer's review found overwhelming evidence that maternal age was not an independent predictor of intrauterine growth, but is likely to exert its effect indirectly through other factors.

A number of studies have used routinely collected data to look at the influence of maternal age on birthweight. These studies generally show an increase in risk for younger mothers (usually adolescents) and older mothers (over 35 years of age) of LBW and SGA and also show that these two groups of women have infants with lower mean birthweights. One of these studies also showed that for younger women (but not older women), the risk was even greater if they were multiparous.

In studies where potential confounders such as parity, ethnicity and socio-economic status were controlled for, a number have found that at the univariate level younger and older mothers had an increased risk of having smaller infants. After controlling for these potential confounders, some of these studies have no longer found significant relationships. A further study has even shown no relationship between maternal age and any measure of fetal growth or body proportionality, except with birthweight ratio
(the ratio of observed to expected birthweight) at the univariate level. In addition, one study has shown an increased risk of SGA for the infants of younger mothers while another suggested an increased risk only for those of older mothers.

The relationship between maternal age and birthweight is likely to be associated with smoking and the possible cumulative effect of years of smoking. The results of studies looking at this relationship show risks increasing with increasing maternal age and amount smoked. One of these studies also showed that, amongst non-smokers, IUGR rates decreased and mean birthweight increased with maternal age. The differences in birthweight and rates of IUGR were also significantly different between smokers and non-smokers in most age categories. However, a study from Washington state in the US found an increasing risk with maternal age in both smokers and non-smokers.

Another study in France looked at the decrease in the rate of SGA from 1971 to 1985 and found a significant decrease in the percentage of mothers 20 years of age and younger and of mothers 35 years or older during this time period. After controlling for other factors maternal age no longer played a significant role in the prediction of the decrease in SGA.

Table 1.9 shows the effects of maternal age in the studies reviewed. Overall the majority of evidence points to the fact that any effect of maternal age is small and not clinically significant or is indirect. It is nevertheless an important confounding variable that needs to be controlled for in analyses.

1.2.4.2 Maternal Hypertension

A recent consensus statement from the Australasian society for the study of hypertension in pregnancy defined hypertension as:

1. Systolic blood pressure $\geq 140$ mmHg and/or diastolic blood pressure $\geq 90$ mmHg.

or

2. Rise in systolic blood pressure $\geq 25$ mmHg and rise in diastolic pressure $\geq 15$ mmHg from blood pressure reading before conception or in first trimester (confirmed by 2 reading six hours apart).
and pre-eclampsia as:

1. Hypertension developing after 20 weeks of pregnancy.
2. Normal blood pressure before pregnancy (or 1st trimester if not known).
3. Absence of history of hypertension or renal disease.
4. Return of blood pressure to normal within 3 months post-partum.

Kramer suggested that it was important to control for maternal height, weight and age when analysing the effect of maternal blood pressure. A study in Oxford by Ounsted et al. found an increased risk of a small for dates infant for both hypertensive and pre-eclamptic women compared to normotensive women. After controlling for confounders, including smoking and maternal height and weight, their respective risks were 2.9 (95%CI=2.0,4.4) and 18.7 (95%CI=7.2,48.5). Similar risks have also been found by other studies at the univariate level. Mor-Yosef found an increase in LBW rates to 6.9%, 15% and 41.1% for those mothers with mild, moderate and severe hypertension. Callan and Witter also found a significant effect with blood pressure (p<0.001), however this was not significant in the younger (<28) and older (>42) age groups although these groups contained small numbers.

Likewise, Mavalankar et al in a case-control study in India found a significant relationship between term LBW (<2500g) and maternal diastolic blood pressure. This study also demonstrated an increasing risk with increasing blood pressure after controlling for socio-economic, maternal biological, antenatal, and intrapartum factors (tobacco was not controlled for due to no effect univariately since there was very low consumption, <2%). The LBW risk was 2.1 (95%CI=1.5,3.0) for infants of mothers with a diastolic measurement of 100-119 mmHg and 8.0 (95%CI=3.2,20.4) for those with a diastolic pressure of greater than or equal to 120 mmHg, in comparison to those with pressures less than 100 mmHg.

These studies show consistent evidence of an increased risk of lower birthweight amongst mothers with hypertension in pregnancy. The risk increases with increasing blood pressure and is much larger for infants of pre-eclamptic women.

1.2.4.3 Maternal Psychological Factors

Maternal psychological factors include depression, life change events, and anxiety. One of the commonly encountered problems with measurement of these events is the time period when they are measured. Stress and anxiety should be measured before the onset of labour or pregnancy complications, or focus on
independently verifiable events. The studies that Kramer reviewed were unable to find any effect of these variables on either birthweight or IUGR. Studies looking for effects on birthweight due to psychological factors should control for ethnicity, age, socio-economic status, parity, smoking, and alcohol.

Several studies have shown relationships between psychological factors and other variables that may be related indirectly to birthweight, but no direct relationship with birthweight itself. Stevens-Simon & McAnarney found that pregnancy during adolescence was more emotionally stressful than later in life. Whilst MacDonald et al found that married mothers were less likely to be depressed and had fewer life events.

Measuring psychologic workload (defined by measuring a job's pace), Homer et al found women who did not aspire to work outside the home, and who had high stress jobs were at higher risk of delivering a SGA infant and had infants with lower mean birthweights. No effect was found for those who did aspire to work outside the home. Increased risks of fetal growth retardation have also been shown with increasing psychosocial scores. Further analysis showed however that this effect was only a good indicator in women with a low BMI(<22kg/m²).

The effects of psychological factors are unclear from the research previously conducted and further work is clearly needed in this area.

1.2.4.4 Sexual Activity

Kramer in his review pointed to both the difficulty and lack of work done in relation to IUGR and sexual activity during pregnancy. The major problems lie with the timeframe in which the data is collected, since sexual activity may be recalled as an "explanation" for a small infant. There is a distinct lack of evidence as to whether any relationship exists between sexual activity and birthweight at this point in time. Studies looking at the effect of sexual activity should control for age, socio-economic status, and genital tract infection.

1.2.4.5 Genital Tract Infections

Genital tract infections are usually with organisms such as; chlamydia trachomatis, mycoplasma hominis, ureaplasma urealyticum, gardnerella vaginalis, trichomonas vaginalis, and candida albicans. Some of which are normal vaginal flora, and are frequently cultured from pregnant women. One of the main issues of the
relationship between these organisms and pregnancy outcome however is the time of infection. The studies reviewed by Kramer were not conclusive in this area, however there was reasonable evidence of no effect on birthweight from M. hominis. Factors that need to be controlled when assessing genital infection are; maternal age, socio-economic status, parity, and treatment for the infection.

Subsequent reviews have suggested no or small effects of genital tract infections on birthweight. Harrison looked at 10 prospective studies and found only one that showed any relationship between M. hominis and LBW. Another review by Romero et al considered studies investigating the relationships of colonisation with M. hominis or U. urealyticum. They found that only two of eight showed any relationship between M. hominis and LBW and none of nine studies showed a relationship between U. urealyticum and LBW.

Other studies have shown similar results to these reviews. A large study in the United States found slightly increased risks at the univariate level for infection with C. trachomatis or C. albicans, however the individual results for SGA and preterm birth were unclear. Berman et al found no relationship between LBW and C. trichomonas or U. urealyticum. There was also no significant association found with M. hominis, although further analysis found an increased risk with M. hominis among women with a history of spontaneous abortion OR=9.4 (95%CI=1.1,8.4). Joshi et al found an increased rate of LBW amongst women who had group B Streptococcus positive swabs (15%) compared to the hospital as a whole (8.7%).

The reviews point to no effect from genital tract infections and further work shows concordance with this. However, the possible interaction between genital tract infection and spontaneous abortion may be worth further study.

### 1.2.4.6 Urinary Tract Infections

Bacterial infection of the urinary tract could spread to both the placenta and the amniotic fluid. The review by Kramer found few studies had examined the effect of urinary tract infections adequately, due to lack of control for confounding variables. Those that had adjusted for confounders were at odds with each other. Any effect that infection by asymptomatic bacteriuria may have on birthweight seems to be small, and with low prevalence (4-7% in normal pregnancy) it will only account for a minor proportion of LBW infants. As for genital tract infections, factors that need to be controlled for are; maternal age, socio-economic status, parity, treatment for the infection, and presence of a genital tract infection.
Romero et al conducted a meta-analysis of studies from 1966-1986 that had reviewed the relationship between prematurity or LBW and asymptomatic bacteriuria. The criteria for the studies to be reviewed included 1) numerical data available, 2) clearly defined asymptomatic bacteriuria, and 3) a control group in treatment trials. After excluding studies that did not comply with these criteria, they found that women who had not been exposed to infection, were at a decreased risk of having an LBW infant compared to women who had untreated bacteriuria. This review also showed that those who had a urinary tract infection and were treated with antibiotics were at approximately half the risk of having an LBW infant than those infected and receiving a placebo.197

1.2.4.7 Antenatal Care

Antenatal care may have beneficial effects on intrauterine growth by reducing or eliminating risk factors such as high blood pressure and UTI. Kramer felt that factors that needed to be controlled for are; ethnicity, weight, age, socio-economic status, parity, smoking and alcohol. The timing of the first visit and the number of visits may be of importance since any pregnancy related problems may be able to be moderated. The quality of antenatal care is difficult to assess and can only be analysed from a randomised clinical trial point of view.

Kramer in his review found that no firm conclusions could be drawn from these studies as to the benefits on timing or number of antenatal visits on intrauterine growth. Similarly, his review found no clear beneficial effect of the quality of antenatal care.120

Gould & Leroy found that no, or only third trimester, prenatal care was associated with socio-economic status (as measured by income) which in turn is associated with birthweight. This suggests that lower SES groups are less likely to have prenatal care.92 Similar results have been reported by Buescher et al, although after controlling for a larger number of variables; including race, marital status and education, the effects of antenatal care on birthweight were no longer significant.44

A number of studies have reported an association between birthweight and antenatal care at the univariate level.108,112,232 Viegas et al found a decreasing risk of LBW with increasing numbers of antenatal visits at the univariate level.232 Insler et al also found an increasing rate of LBW with decreasing antenatal care especially among those receiving no or only rudimentary care.108 After controlling for age, race, marital status, education, and parity, Lee et al found an increasing risk with greater inadequacy of antenatal care133 as determined by the Kessner index.112
Greenberg et al found that the strongest association between prenatal care and birthweight was amongst the group with the lowest rate of LBW, though prenatal care still had a significant effect after controlling for maternal education and race. However, they considered that social status is unlikely to be responsible for all of the effect of prenatal care.³³

Scholl et al found that amongst adolescents increasing prenatal care, as measured by the Kessner index, was associated with increasing birthweight. Adjustment for pre-pregnancy weight, height, age, clinic payment status, gravidity, ethnicity, smoking, drinking, and complications of pregnancy, rendered these differences insignificant.²⁰⁵ Similarly, Kramer found no effect of the timing of the first prenatal care visit during the first trimester, nor of the number of prenatal visits, nor of attendance at prenatal classes on any body measurements.¹²² A summary of the effects found in association with antenatal care can be found in Table 1.10.

1.2.4.8 Antepartum Haemorrhage

Voigt et al studying the relationship between smoking, abruptio placentae, and SGA, found a significantly increased risk of SGA of 2.6 in women with abruptio placentae, which was identical for smokers and non-smokers.²³⁶

In a study of women who had placenta previa, Wolf et al found no significant difference in the proportion of SGA infants or in mean birthweights.²⁵¹ Another study conducted by Brar et al found that placenta previa women were more likely to have an IUGR infant as well as other adverse pregnancy outcomes.⁴⁰

Because of the limited number of studies conducted, the relationship of ante-partum haemorrhage variables to infant birthweight is still unclear and further study is necessary.

1.2.4.9 Inter-Pregnancy Interval

Inter-pregnancy interval is defined in different ways. Some define it as the time interval from birth to birth (which in reality is the birth interval), whilst others define it as the interval from birth to conception, which avoids the problems posed by the length of pregnancy.¹²⁰ The latter is a more relevant definition as conception is the point of time from which birthweight starts to be determined.
Kramer's literature review suggests that the most obvious biological mechanism by which short pregnancy intervals affect birthweight would be nutritional depletion (although inadequate physiological recovery could occur for other reasons). He also suggests that pre-pregnancy weight should not be controlled for, since any effect of small pregnancy interval on intrauterine growth may act by depleting maternal fat stores. The potential confounders that he does believe should be controlled for are: ethnicity, socio-economic status, parity, and prior LBW or preterm infants. The studies that Kramer reviewed had not adequately studied the effect of inter-pregnancy interval on gestation, but did indicate that it had no effect on intrauterine growth.

Studies that have looked at inter-pregnancy interval have used different interval categories when looking at the effects of the length of the interval. Ferraz et al in Brazil found a small increase amongst women who had an interval of six months or less compared to those with intervals over a year OR=1.38 (95%CI=1.02,1.86) (though this increase was not significant if maternal weight was in the model, OR=1.25 (95%CI=0.91,1.72)). A higher proportion of these women had lower body weights, which suggests that they may have had insufficient time to restore their nutritional reserves. Similarly, in the US, Klebanoff found differences in birthweights and risks of SGA for those with intervals less than three months, though these risks did not remain significant after controlling for confounders including maternal weight. In summary he stated:

"A short inter-pregnancy interval exerts itself through the baseline risk profile of the mother, i.e. the women who had short intervals were at high risk of a LBW infant before the interval even began."

Other studies have also suggested increased risks associated with shorter intervals between pregnancies. It seems therefore that a short inter-pregnancy interval acts in two ways: 1) The mothers tend to be in high risk categories of other risk factors e.g. smoking, socio-economic status, and age; and 2) full recovery of physiological factors or nutritional reserves is not achieved, which in turn has an impact on the size of the new fetus.

1.2.4.10 Parity

There are two areas of interest related to parity, the first one being that of primiparous pregnancies which are usually considered to have less favourable outcomes than multiparous pregnancies. The second is that of grand multiparae, the consequences of which little is known. With parity and age being closely related it is
essential to control for maternal age when considering any effect due to parity. Other variables that should be controlled for are; ethnicity, socio-economic status, and a prior LBW or preterm infant.

Kramer in his analysis showed clear results in regard to IUGR. In general, mean birthweights increased with increasing parity; the sample size weighted effect being 43.3g/birth; a comparison of primiparae versus multiparae births found a difference of 82.7g. The relative risk for primiparae mothers compared to other mothers was not large (OR=1.23).120

A number of studies have found the expected relationships between parity and birthweight, with primiparous mothers giving birth to smaller infants. Two studies using routinely collected data have shown increased risks associated with primiparity.164,232 Other studies that have controlled for confounding variables, as mentioned above, have also shown increased risks, whether the comparison group be non-primiparity or any grouping of previous pregnancies, with the odds ratios usually below 2.66,75,133,240 Similarly, Gardosi's study only found a difference of 53g below the population mean for primiparous mothers.83 However, these studies found no differences in birthweight between later pregnancies.

As far as grand multiparae is concerned, studies in general show no increased risk for poor birthweight outcomes, with no significant differences between multiparous and grand multiparous mothers.75,133,164,207,240 Furthermore, Seidman et al showed that any increased risk was likely to be due to socio-economic status by showing a difference in risk of SGA among two groups of grand multiparae women.207 The differences from the population mean of birthweight amongst grand multiparae women varied greatly at each parity in a study by Gardosi.83 One study did find a slightly increased risk for grand multiparous mothers, though it used routinely collected data and was hence unable to control for confounders.200

In summary, there seems little doubt that there is an effect of primiparity on birthweight (Table 1.11). However, subsequent pregnancies, including those of high order, seem to have little direct effect on birthweight.

1.2.4.11 Previous preterm, IUGR, LBW or SGA infants

Some women have repeated SGA births, which may be inherent or could indicate the persistence of other risk factors. Kramer's review was unclear on the independent effect of prior outcomes on the current infant.120 Kramer suggested that the variables which needed controlling for in analyses were; height, weight, age, parity, weight gain or caloric intake, smoking, and alcohol.
A number of studies have shown an increased risk of a small infant where the previous infant was born small. Two studies, found that mothers who had previously given birth to a small infant had infants which were even smaller than those of primiparous mothers.\textsuperscript{91,113} Goldenberg found a mean birthweight of 3107g for mothers with a previous LBW infant, and 3214g for primiparous mothers after controlling for gestation, sex, race, age, height, weight gain, BMI, hypertension, smoking, alcohol and drugs; these were significantly different (p<0.001). Similarly, Khoury reported a SGA risk of 3.59 (95\% CI=1.79,7.20) for mothers who had already had a small infant after controlling for age, race, gravidity, prenatal care, marital status, fathers education, and infant sex. An analysis restricted to multiparous women found that mothers with a previous small infant also had an increased risk of having another.\textsuperscript{113}

Other studies have also shown effects of where the mother has previously had small infants, though the point estimates of these risks have differed in size. Ferraz et al found an increased risk of 2.42 (95\% CI=1.79,3.29) after controlling for inter-pregnancy interval, age, history of fetal loss, smoking (in the index pregnancy), education, and post-partum weight.\textsuperscript{76} While Ounsted found a much larger risk of 7.0 (95\% CI=4.1,12.1) after controlling for smoking, hypertension, primiparity, height, weight, weight gain, and congenital abnormalities.\textsuperscript{175} A study by Wen et al also found an increased risk of an IUGR infant where the previous infant had been preterm (OR=1.44, p<0.05).\textsuperscript{240}

Similarly, Hoffman et al found an increased risk for mothers who had a single previous pregnancy that had resulted in a SGA infant. The risk was similar for those mothers who had had two previous live births one of which was SGA. The odds ratio was 2.1 if the first had been SGA, and 2.7 if it was the second infant. However, the increased risk was higher if both of the infants had been SGA (OR=5.0).\textsuperscript{104} This study points to the expected effect of the increase in birthweight with parity though birthweight seems to be starting from a lower level in mothers who have previously had a small infant.

Read & Stanley found that a number of the factors that predicted the risk of a repeat SGA were in fact the same as those that predicted the risk of an isolated SGA infant, namely; weight loss in pregnancy, prolonged rupture of the membranes, less than 20 years of age at the first birth, smoking, education, and maternal birthweight less than 3000g. However, point estimates of these risks differed and were stronger for the group of mothers with repeat SGA deliveries.\textsuperscript{191}

In summary, there seems to be an increased risk of a SGA infant if the outcome of a previous birth has been preterm, SGA or LBW. The fact that factors predicting recurrent bad outcomes may be due to the same pre-
disposing factors makes determination of which factors are affecting all pregnancies (e.g. smoking) and which only some pregnancies (e.g. maternal nutrition) difficult without good quality data.

1.2.4.12 Previous Spontaneous Abortion

Kramer's review identifies the many difficulties associated with the relationship between previous spontaneous abortion and SGA due to the increasing advancement of technology. Spontaneous abortion now overlaps with pre-term delivery, and it may be appropriate to treat them as a continuum. Such events also make it difficult to determine and control for parity. The decision to control or not, depends on whether the improved outcome of second pregnancies is influenced by prior conception, or by the enhanced uterine blood flow and anatomical enlargement that occurs only during the third trimester. Variables that Kramer therefore decided needed controlling for were; weight, parity, gestational weight gain or caloric intake, smoking, and alcohol. The review suggests from the data available that there is no effect on birthweight or an increase in risk of an IUGR infant from previous spontaneous abortions.\textsuperscript{120}

Analysis of routine data collected in Scotland found women who had previously had a spontaneous abortion to be no different to that of primiparous women (OR=1.02). However, gravidae 2 women showed a decreased risk (OR=0.68, 95%CI=0.64,0.71) suggesting gravidae 2 women are different to those with a spontaneous abortion.\textsuperscript{187} A further study suggested an increasing risk with increasing numbers of spontaneous abortions in both otherwise primiparous women (OR=1.30 for 1 abortion and OR=2.01 for 2 or more) and in multiparous women (OR=1.24 for 1 abortion and OR=2.04 for 2 or more).\textsuperscript{186} However, one study found no effect on SGA of any number of spontaneous abortions, (univariate OR=0.95, 95%CI=0.90,1.00)\textsuperscript{16}, and another looking at LBW found risks of 1.04, 0.72 and 0.62 for 1, 2 and 3 or more abortions respectively.\textsuperscript{232}

In general, the overall effect of previous spontaneous abortions seems to be unclear and further work in this area will help to resolve these issues. Any effect may well be working at different levels in multiparous mothers and those who would otherwise be primiparous.

1.2.4.13 Previous Induced Abortion

As in the case of spontaneous abortion the main question centres around the number of abortions. Controlling for parity also has the same uncertainties. However when possible; parity, genital tract infections,
smoking, and alcohol should be controlled for. The studies reviewed again show no evidence of an effect of induced abortion on intrauterine growth.\textsuperscript{120}

A number of studies looking at the risk of induced abortions have used routinely collected data. Some studies have shown no increased risk from the number of induced abortions. Viegas found risks of 0.8, 0.93, and 1.71 for 1, 2 and 3 prior induced abortions at the univariate level, none of which were significant.\textsuperscript{232} Pickering found odds ratios of 0.90 and 1.13 respectively for 1 and 2 previous induced abortions compared to primigravid women.\textsuperscript{187} In another study, Pickering found an increased risk of an infant <2500g amongst both otherwise primiparous (OR=1.20 (95\%CI=1.08,1.34)) and multiparous mothers (OR=1.32 (95\%CI=1.19,1.47)) that had one or more previous abortions compared to those without a previous abortion.\textsuperscript{186} Studies that have been able to control for other confounders including age, parity, marital status, socio-economic status, and ethnicity have generally found an increased risk at the univariate level but found no increase in risk once confounders including smoking and parity had been controlled for.\textsuperscript{16,136,208}

On the other hand, a study by Bracken et al found that induced abortion of the first pregnancy did not affect the mean birthweight or risk of LBW infants in comparison to first delivered infants. Those delivering their second live infant had higher birthweights compared to those in their second who had aborted their first pregnancy. Hence infants of women who are pregnant for the second time after the first pregnancy has been aborted have infants of similar birthweights to infants of women who are having their first pregnancy. In women who have had two previous abortions the effect on birthweight was not much greater than that seen for one previous abortion. An intervening pregnancy after an induced abortion increased birthweights of the 3rd pregnancy.\textsuperscript{39}

Like the effects of spontaneous abortions the effect of induced abortions is a little unclear, though the patterns are similar. It is uncertain whether spontaneous and induced abortions are similar as far as their consequences are concerned, and whether they could be combined for analysis.

\subsection{1.2.4.14 Previous Neonatal Death/Stillbirth}

Kramer’s review found that a prior stillbirth or neonatal death may be a proxy for LBW (mainly relating to pre-term) and not for IUGR.\textsuperscript{120}

In Scotland using routinely collected data, two studies have found that mothers having one or more previous perinatal deaths were at an increased risk of giving birth to either a LBW or a SGA infant.\textsuperscript{186,200}
Meanwhile Ferraz found no association of giving birth to an IUGR infant after having a previous neonatal death. Likewise Algert et al found no difference in risk of an SGA infant among mothers who had a previous stillbirth or neonatal death. Hence the effects of these outcomes is also still unclear.

1.2.4.15 Prior Infertility and In-vitro Fertilisation

Williams et al found that the subfertile women, as defined by the failure to achieve a clinically recognised pregnancy within 1 year of unprotected intercourse, were at an increased risk of delivering a term LBW infant (OR=2.3, 95%CI=1.2,4.4) compared to fertile women. Likewise Doyle et al, in a report from the Medical Research Council In-Vitro Fertilisation Register, found that women who have received in-vitro fertilisation are more likely to have adverse pregnancy outcomes. Whether the fertilisation resulted in a multiple or single birth, they found increased rates of preterm, LBW, and SGA infants. Hence there is a suggestion that sub-fertile women may be at an increased risk of giving birth to SGA infants.

1.2.5 Nutritional Factors

Nutrition both before and during pregnancy is likely to play an important part in the growth of the fetus. Nutrition before conception may well be important, however, pre-pregnancy weight has previously been considered under genetic factors. Nutrition throughout pregnancy takes many forms which have the potential to affect fetal growth. Those that will be considered below are; 1) weight gain during pregnancy, 2) caloric intake, 3) protein intake, 4) iron, and 5) zinc and copper. Energy expenditure also needs to be considered, since nutritional intake needs to be sufficient for the mother, the fetus, and any energy expenditure required by exercise or work.

All of the variables discussed in this section require control of ethnicity, height, weight, age or parity, socio-economic status, smoking, and alcohol consumption. Any additional variables that should be controlled for will be mentioned in the appropriate section.

1.2.5.1 Maternal Weight Gain

Kramer's review of pregnancy weight gain views this variable as being additive to that of pre-pregnancy weight. This is due to the fact that maternal energy stores are a major source of nutrition to the fetus, hence
stores that are present prior to pregnancy are seen to be of additional benefit. As such, nutritional stores are
seen as a gain in weight the mother does not need to make during pregnancy. Readily available sources may
also be advantageous in comparison to sources that must be gained or acquired.

Kramer found that weight gain during pregnancy had a positive effect on birthweight, the sample weighted
average effect being 20.3g per kg of weight gain. Kramer also suggests that if one is to correlate
birthweight with weight gain, the infant’s weight (and placental weight) should be subtracted from the weight
gain. The studies reviewed show that undernourished women reap a greater benefit than other women for the
same weight gain.

Weight gain is often measured as grams per week due to the differing lengths of gestation, but it is also
measured as overall weight gain during pregnancy. Kramer believes the former is the better way of
measurement because of the effect of gestation. Another problem that occurs with calculating maternal
weight gain is that knowledge of pre-pregnancy weight is required.

Hediger et al, in looking at the effect of weight gain during adolescent pregnancy, found a number of
associations. Mothers of their study were placed into the following groups: adequate weight gain throughout
pregnancy, inadequate weight gain in early pregnancy, inadequate weight gain in late pregnancy, and
inadequate weight gain in both early and late pregnancy. All three of the inadequate weight gain categories
were associated with increased risks of SGA. This was confirmed further in another study and hence
they have suggested in a further publication that:

"Current targets for adult gravidas are total weight gains of 9-14kg by term(> =37 weeks
gestation) to minimise the risk of LBW and infant morbidity. However, larger weight gains of 14-
18kg may be appropriate for pregnancy during adolescence, because adolescents seem to transfer
less of the weight they gain to the fetus than do adults."}

The same authors have also reported that after dividing mothers into groups according to pre-pregnancy
BMI (underweight (<19.5kg/m²), normal (19.5-24.5kg/m²) and overweight (>24.5kg/m²)), the magnitude
of weight gain increments at twelve and twenty weeks of pregnancy, as well as overall weight gain, did not
differ between the groups. They found that increased weight gain in women with low and normal BMI's
improved birthweight more than in women with a high BMI. Similar effects have also being suggested by
others though one of these found that the effect was weak amongst Whites. In a further paper,
Kramer et al found that each 5kg net gestational weight gain increased birthweight by 1-2% of mean birthweight.122

Several authors have also found that, when you compare the weekly weight gain of women, those who have low and very low weekly weight gains are at increased risks of having small infants.8,64,240 Further to this finding one of these studies also showed that if weight gain in the second half of pregnancy was high after inadequate gain in early pregnancy, there was still an increased risk, although this did not reach significance.240

A review of maternal anthropometry summarised that pre-pregnancy weight and weight gain are independent and completely additive in their effect on birthweight. Therefore optimal weight gains are different for women who begin pregnancy at different nutritional levels.123 In line with this, the American Institute of Medicine has published guidelines which suggest what appropriate weight gains during pregnancy should be224:

"12.5-18kg for a pre-pregnancy BMI<19.8, 11.5-16 kg for BMI 19.8-26.0, 7.0-11.5kg for BMI 26.0-29.0, and at least 6kg for BMI's >29."

Parker & Abrams have shown that compliance with these guidelines reduced the risk of having an SGA infant.176

Weight gain in pregnancy clearly plays an important role in determining birthweight though it is heavily confounded with such variables as pre-pregnancy weight, and BMI. There is a clear indication that the timing of poor nutrition also plays a major role in the effect on birthweight, with poor weight gain in early pregnancy seemingly having a more detrimental effect than poor nutrition in late pregnancy.

1.2.5.2 Caloric Intake

Caloric intake during pregnancy is related to gestational weight gain, but has the disadvantage that it takes no account of energy expenditure and it is difficult to measure with accuracy. It has the advantage, though, of being open to intervention. Data on the importance of the timing of caloric intake during pregnancy is unclear. Kramer found the sample size weighted effect of supplementation in undernourished women to be 99.7g/100 kcal/day and 34.6g/100 kcal/day in well nourished women. He found estimation of the risk reduction of IUGR to be approximately 0.47 for undernourished women and 0.82 for well nourished women.120 Additional control should also be made for work during pregnancy and protein intake.
A number of studies have shown little relationship between caloric intake and birthweight. Villar et al found no effect of low energy supplementation (<33.2 kcal/day) (OR=1.11 (95%CI=0.79,1.59)), or of varying amounts, while Arbuckle & Sherman showed an effect at the univariate level only. Similarly, Hediger et al found no effect of low energy supplementation (<33.2 kcal/day) (OR=1.11 (95%CI=0.79,1.59)), or of varying amounts, while Arbuckle & Sherman showed an effect at the univariate level only. Similarly, Hediger et al found a relationship between deficits in carbohydrates on gestational weight gain but not on birthweight, LBW or preterm delivery. This suggests that the relationship between nutrient intake and these outcomes may be indirect and moderated by gestational weight gain.

Smith looked at the effects on birthweight amongst infants who experienced famine in utero during the second world war in Holland. He found that infants exposed during the third trimester to famine in utero had the largest decrease in birthweights. A follow-up study of women who had been exposed to the famine in utero found that those exposed during the first and second trimester of pregnancy went on to deliver infants whose birthweights were lower than those women who were not exposed to the famine in utero. There were no differences seen in the birthweights of infants born to mothers who had experienced their exposure to the famine during the third trimester of pregnancy.

The evidence suggests that caloric intake does not seem to have any direct effect on birthweight, although it may well act indirectly through weight gain. Some groups (particularly smokers) have been shown to have lower intakes of almost all nutrients. As such, these variables are also likely to confound any effect of caloric intake.

1.2.5.3 Protein Intake and Status

Kramer’s review looked at studies on protein intake and status, but like those on caloric intake they were mostly intervention studies. However, maternal protein intake or status was concluded not to have any effect on intrauterine growth after adjustment for caloric intake. It is essential to control for gestational weight gain or caloric intake when analysing the effect of protein intake or status.

Studies looking at protein have found very little effect on LBW. However, Scholl et al did find that protein intake was related to gestational weight gain and hence the effect may again be indirect. Haste et al also reported that protein intake was lower in smokers than non-smokers, but this was of borderline significance (p<0.07) when considered as grams per 1000 kcal of the diet, which was used as a measure of quality of diet.
1.2.5.4 Iron and Anaemia

Haemoglobin concentrations fall until about the 32nd week of pregnancy. Anaemia may impair oxygen supply to the fetus and hence result in changes in fetal growth. Iron deficiency without anaemia could also lead to poor pregnancy outcomes. Kramer found however that few studies had adequately studied the relationship between iron and anaemia and these studies showed no significant effects on birthweight. As for protein intake, it is essential to control for gestational weight gain or caloric intake when analysing the effect of iron intake or status.

Higher anaemia rates are often found in lower socio-economic groups and reports have also been made of higher levels amongst Blacks, whilst Haste et al have also reported lower iron intakes amongst smokers.

Knotterus et al found a J shaped relationship between both haemoglobin (Hb) and haematocrit (Ht) levels and LBW in the infants of mothers they studied. Mothers with the lowest levels of Hb or Ht had slightly higher rates of LBW. Mothers with Hb≥8.0mmol/l (high levels) had a LBW rate of 15% compared to 3.9% in the group with Hb between 7.0mmol/l and 7.9mmol/l (average). Similarly mothers with Ht>38% had a LBW rate of 13.3% compared to 4.2% in the group with Ht between 33 and 37%. Mothers with high erythrocyte counts had a higher rate of LBW but there was no difference in LBW rate associated with mean cell values (MCV).

Mavalankar et al found that women who had either moderate or severe anaemia where at increased risk of a term LBW infant. Those with moderate anaemia had an increased risk of 1.8 (95%CI=1.4,2.4) and those with severe anaemia an increased risk of 5.6 (95%CI=2.1,15.3) after controlling for a large number of variables.

1.2.5.5 Zinc and Copper

Kramer found few studies that discussed the effects of zinc and copper on pregnancy outcome. The data available suggested that neither zinc nor copper had any important effect on intrauterine growth. It is essential to control for gestational weight gain or caloric intake when analysing the effect of these variables. It has also been established that undernourished individuals have impaired immune responses and this can be due to undernourishment of single nutrients such as zinc and copper. Kuhnert, however found that maternal zinc intake during pregnancy was not related to the mother’s zinc status but to that of the fetus.
Neggers et al in studying Black and White ethnic groups in America reported that maternal zinc levels decrease during pregnancy. Also of note was that Black mothers had lower concentrations than Whites. There was a significant correlation between birthweight and zinc concentrations in both Blacks ($r=0.28$, $p=0.0001$) and Whites ($r=0.38$, $p=0.0001$). Haste et al have also reported lower intakes of both copper ($p<0.01$) and zinc ($p<0.05$) amongst smokers.

Simmer found that mothers of SGA infants had significantly lower levels of birth polymorphonuclear (PMN) and mononuclear (MN) cell zinc contents than mothers of AGA infants twenty four to forty eight hours after delivery. PMN levels were also lower in smokers. Simmer has also found a lower dietary intake of zinc in mothers of SGA infants in comparison to mothers of AGA infants.

### 1.2.5.6 Other Vitamins and Minerals

Arbuckle & Sherman found a univariate relationship between serum Vitamin A and SGA; however after controlling for other variables the difference was insignificant.

Skajaa et al found there were no differences in the average magnesium intakes in the normal, pre-eclamptic, SGA or preterm pregnancies, and neither were there differences in the level of magnesium absorbed.

### 1.2.5.7 Energy Expenditure, Work, and Physical Activity

Maternal activity varies greatly and can be associated with either normal household activity, working in a workplace, or maternal exercise. Kramer found that the effect of maternal work on IUGR was uncertain especially in the developed world as most studies in this area have been carried out in developing countries where work is likely to be more physically strenuous and caloric intake already low.

A number of studies have found no increase in risk between work and birthweight. No difference has been found between light or heavy work, the number of hours worked, or the number of hours spent standing. No differences have been found between women in full time employment and those not in paid work. Nor did duration, effort required, or energy expenditure in either paid work or work at home have any effect on LBW. A possible reason for the lack of effect seen in these studies may be due to the “healthy
worker effect", i.e. the women who are healthy are the ones that are able to work, and those that aren't working aren't able to.

On the other hand Barnes et al have found an effect of standing while carrying out work in the home with the risk increasing with the length of time standing, with a decrease in birthweight of 121g for women who spend 50% of time at home erect.32 Peoples-Shep et al also reported a slightly increased risk for those women working forty or more hours per week (OR=1.70, 95%CI=1.03,2.68)181 and another study reported small increases in risk associated with heavy lifting in the workplace and shiftwork, but no effect of long working hours or fatigue.21

There is still no good data that clearly points to the consequences of work or physical activity during pregnancy. There may be some effect of long working hours doing heavy physical work.

1.3 Causal Pathways Relating Intrauterine Growth Retardation to Placental Function

The placenta can be defined as "any union between fetal and parental tissues for the purpose of exchange of gases and nutrients." 162 The development of the placenta is dependent not only on the genetic information within the fetus but also on maternal adaptation to factors that facilitate the development of the placental bed. Central to placentation is the requirement of the invading placenta to establish a blood supply with the mother.6

The placenta is a specialised organ of exchange between the fetal and maternal circulations to provide nutrients and oxygen to the fetus and excrete waste products. Nutrient and oxygen supply to the fetus are the most important regulators of fetal growth.97 The placenta also has considerable metabolic activity consuming large amounts of oxygen and glucose, normally consuming approximately 2/3rds of the oxygen and 1/2 the glucose uptake of the conceptus. Reduced substrate supply from the uterine circulation, therefore, also requires metabolic adaptation by the placenta as well as the fetus.97 The placenta is vital to the survival of the fetus providing nutrition, oxygenation, exchange and various metabolic functions.162

The basic structure of the relationships in pregnancy is shown in the figure below. As can be seen from this schematic diagram, the placenta controls nutrient transfer via the uterine and umbilical vasculatures between the mother and the fetus during pregnancy.
Placental transfer occurs by a large variety of mechanisms, each unique for a specific substance (or group of substances with similar physical-chemical properties). The direction and magnitude of the rate of transfer of a substance across the placenta depends on both the maternal and fetal arterial concentrations of the substance. These concentrations are not due just to the placenta but also to such things as maternal diet, hormonal status and metabolic rate of the substance.

At different stages of gestation the relative growth rates of the placenta and its fetus vary greatly. In early pregnancy the placenta grows at a quicker rate than the fetus, however in the period from 22 weeks of gestation to term there is a 7 fold increase in fetal weight and a 2 fold reduction in surface area of the placenta relative to fetal weight. Fetal weight is directly related to placental weight in late gestation, experimental work has demonstrated that fetal growth is in fact dependent on placental growth. It has also been noted that caution should be taken in cross species comparison of placental growth and function.

Furthermore, small, average and large fetuses are directly related to small, average and large placentae, indicating that ordinarily the fetus does not outgrow the placenta. It is hypothesised that the fetus grows within the limits set by the placenta, yet there are few studies of the morbid anatomy of the placenta that have tested this hypothesis. In late gestation, however, fetuses with relatively small placentas do tend to outgrow their placenta and the fetal-placental weight ratio becomes higher than normal.

Fig. Schematic diagram of transfer between mother, placenta and fetus

Mother

Placenta

Fetus

Uterine blood flow

Umbilical blood flow
Proper function of the fully formed placenta during the fetal period (2-9 months) is critical not just for nutrient transport to the fetus, but also as a protective barrier against environmental insults such as smoking. The placenta also protects the fetus by preventing the accumulation of waste products. If the placenta is not functioning properly, it can be the limiting factor not only for fetal nutrition but also for the maternal-fetal exchange of physiological constituents and waste products that represent a pathological risk to the fetus. Hence normal placental growth is a requirement for normal fetal growth.

In recent times the knowledge concerning the development of the human placenta has increased greatly, however cause and effect relationships are still unknown for most common disorders of pregnancy. IUGR has been shown to be associated with reduced capillary development in the terminal villi. The cause of this change is unknown nor is it clear whether this is a primary event or whether it follows defective early implantation resulting in fetal and placental hypoxia.

Winick has claimed that DNA formation (in the placenta) ceases at a mean placental weight of 300g or 2300g fetal weight (35-36 weeks gestation). Since placental weight continues to increase till term, "growth" in the later part of the third trimester must imply an increase in cellular size with no further increase in cell number. At 105 days gestation (15 weeks) placental and fetal weight are approximately equivalent. The dilemma of size and function is most apparent in the IUGR infant. These infants appear to reside on the fringe of adequate oxygenation and nutrition balancing the fetus's survival precariously.

Relative or selective failure of placental growth may lead to an increased fetal weight to placental weight ratio. This is associated with significant risks to the fetus, irrespective of its size. Molteni et al have previously shown that infants who have fetal:placental ratios of 10 or more, and hence may have outgrown their placentas are more prone to distress during labour (and hence have lower Apgar scores). He stated that the extent to which the placenta limits the growth of a fetus is unknown. Thompson et al and Gruenweld have shown that the weight of a placenta is a poor indicator of functional capacity. The increase in fetal distress of these infants points to the fact that placental function is precariously balanced in those infants who must receive their supply of oxygen and other nutrients from relatively little placental tissue.

Similarly Bonds et al have found the incidence of perinatal problems was increased in those infants whose fetal/placental ratio was greater than 11. These infants having higher incidences of intrapartum distress,
meconium stained amniotic fluid, apgar score less than 7 and hyperbilirubinemia. Those with low fetal:placental ratios showed no increased risk of perinatal problems. He also pointed to the fact that these infants have presumably outgrown their placentas.

Ultrasoundography has been used to determine placental volume serially in human pregnancy and small placental volumes at mid gestation were associated with SGA infants. Furthermore, placental growth retardation always precedes fetal complications or growth retardation by at least 3 weeks. Similarly Wolf has shown that in infants who have an abnormal outcome (fetal death, fetal distress requiring caesarean section or SGA) placental growth levels off at a significantly earlier time than fetal growth. The interval between the occurrence of placental and fetal growth reduction showing that the placenta has a certain reserve capacity.

Since small infants tend to have small placentae and large infants large placentae, it implies that this growth pattern for the placenta exists in early pregnancy, possibly determined shortly after implantation and that once this pattern is determined it continues throughout pregnancy.

In fetal growth retardation, there is a decrease in all dimensions of fetal growth, indicating a common cause for the development of all organs of the fetus. One of the requirements for growth and development of fetal organs is essential amino acids for protein synthesis.

In fetal growth retardation, the results of cordocentesis have shown that a significant proportion of these infants are hypoxaemic. This is a chronic state, since a rise in haemoglobin concentration occurs which can be interpreted as an adaptation, which increases the carrying capacity of fetal blood for oxygen. It is also suggested that the association of higher packed cell volume at first antenatal visit with lower birthweights and placental weights probably reflects a relative failure of the mid-trimester physiological haemodilution of pregnancy in women with retardation of fetal and placental growth. Laurini et al have also shown that SGA fetuses are associated with placental infarction which is also known to be related to fetal hypoxia.

### 1.3.1 Effects of Various Factors on Fetal and Placental Growth

Factors influencing placental weight include gestational age, maternal size, infant sex, and multiple pregnancy. Direct experimental evidence for a causal link between limitation of placental growth and reduced fetal weight at delivery was first provided by Alexander. It was demonstrated that increasing
restriction of placental growth led to a greater incidence of growth retardation of the fetus, intrauterine death, or premature birth.

The placenta has received less attention than the fetus, but growth retardation is associated with a greatly reduced area for exchange within the placenta, failure of trophoblast invasion into, and alteration of, maternal arterioles. In the face of inadequate or altered substrate supply the fetus must alter its metabolic patterns and activity if it is to survive.97

Other influences include maternal behaviour or lifestyle factors. Some may be inescapable for the women, such as malnutrition or poor socio-economic circumstances. Others including maternal drug ingestion or smoking, are avoidable. Some of these are considered below.

Naeye has reported that birthweight and placental weight are related to pre-pregnancy weight, race, weight gain in pregnancy, haemoglobin (lowest in 3rd trimester), peak diastolic pressure, weeks since quitting work, parity, and infant sex. Maternal smoking and height are related to birthweight but not placental weight. Taking these factors into account he found that placentae that were underweight for birthweight were associated with high haemoglobin values in neonates and small body size in later childhood. Overweight placentae were also found to be associated with acute antenatal hypoxia, low apgar scores, Respiratory Distress Syndrome (RDS), neurological abnormalities and neonatal death. He also found that relative placental underweight was associated with small body size at 7 years independent of the factors that had the greatest effects on placental weight.166

Other studies have found that placental weights and birthweight/placental weight ratios were significantly related to gestation, gender and ethnicity.68

1.3.2 Maternal Nutrition

Before implantation the local maternal environment partly determines the size of the future placenta, and hence the fetus, and may alter the length of gestation. The development of the early embryo and the maturation of the endometrium has to be closely matched to allow formation of the placenta and its continued growth and development.194

In addition the growth of the placenta is influenced by events occurring before pregnancy. Maternal nutrition, partly through the regulation of ovarian activity, modifies the maternal endocrine environment
required for maintenance of early pregnancy. Furthermore, maternal nutrition before pregnancy influences the impact of variation of nutrition in early pregnancy and subsequently alters the growth rate of the placenta.\textsuperscript{194}

It is important to remember that fetal nutrition and maternal nutrition may not be equivalent in either regulation or effect. In human pregnancy, for example, relatively extreme changes in maternal nutrition are required to cause relatively small changes in size at birth (cf Smith 1947 Dutch famine, see Chapter 1, section 1.2.5.2).\textsuperscript{97}

During maternal undernutrition placental size is often increased. Thus substrate supply across the placenta is unlikely to have been limited in these cases.\textsuperscript{97}

The effects of nutritional insult on placental growth are particularly variable. In general, undernutrition in early gestation has little effect, or may slightly increase placental weight, and under-nutrition in late pregnancy also has little effect, or reduces placental weight. Under-nutrition in mid pregnancy or a change in nutritional status at this time of pregnancy, has been reported to either increase or decrease placental weight. The effect may depend at least in part on the nutritional status of the mother around time of conception. Since placental size itself has an important influence on fetal growth, the impact of the nutritional regulation of placental growth on the subsequent growth of the fetus and its organs remains to be investigated.\textsuperscript{97}

1.3.3 Smoking

The reported effects of smoking during pregnancy on the placenta are conflicting. Naeye in his investigations stated that it was not surprising that placentae were normal rather than undergrown when women smoked during pregnancy since smoking can make fetuses hypoxic. The placenta usually responds to hypoxia by increasing its size as long as the hypoxia is not accompanied by a deficiency of nutrients, as occurs with sustained, low utero-placental blood flow.\textsuperscript{166}

On the other hand, Robinson has reported that maternal tobacco smoking is associated with a different aetiology, with smaller placentas and thickening of the villous membrane in early pregnancy. In late pregnancy there is also a reduction in the capillary volume of the villi and at both stages of pregnancy necrosis of the syncytiotrophoblast is found. These presumably contribute to the reduction in birthweight caused by maternal smoking.\textsuperscript{194}
Placental volume is higher in women who are smokers at conception only, but not in those who continue to smoke through pregnancy.\(^{194}\)

Smoking brings into play many mechanisms which could be responsible for failure of placental and fetal growth. In the placenta, reduced vascularisation, intimal oedema of the capillaries and thickening of the basement membranes of the villi could impair placental function and fetal growth. Relative hypoxaemia due to high interfetal concentrations of carbon monoxide, which competes successfully with oxygen for haemoglobin binding sites, may also contribute to the reduction in fetal growth. Some compensation does occur as haemoglobin concentrations in the mother and fetus increase, but a deficit in delivery of oxygen to the fetus may remain. Other components of smoke, such as thiocyanate or metal ions may adversely affect fetal or placental growth. Changed placental morphology and accelerated maturation of the placenta have been described in response to smoking.\(^{195}\)

The fetus is dependent on the placental transfer of amino acids from maternal to fetal circulations. This is a two step process, firstly the uptake of the amino acids from the maternal blood to the placenta and secondly the diffusion of these amino acids from the placenta into the fetal circulation. The first step is critical and could be depressed under placental hypoxia induced by smoking. Nicotine, carbon monoxide, cyanides and nitrates have all been shown to reduce active uptake of amino acids by the placenta. Hence maternal smoking decreases the net transfer of amino acids from maternal to fetal blood.\(^{218}\)

Compensation for the insult due to the decrease in amino acid transfer takes place in three forms: 1) An increase in placental size. 2) an increase in the number of amino acid carriers to increase the amino acid uptake and 3) a decrease in membrane fluidity of the placental blood vessels so they are less responsive to vasoconstriction.\(^{201}\)

The actions of smoking on the maternal-fetal unit are important since an acute bolus of nicotine produces ischaemia, placental blood flow restriction and fetal hypoxia. In addition smoke itself produces hypoxia due to carbon monoxide, and the anorexic effects of nicotine can also contribute to maternal undernutrition. Although fetal weight is decreased due to maternal smoking, brain growth is spared relative to body weight. This finding is common to a number of fetal insults. The effects on the placenta however are less clear.
Animal studies however suggests that the actions of nicotine do not reflect directly on the fetal nervous system. However experiments have suggested that nicotine without the participation of hypoxia and ischaemia interferes with neuronal maturation and alters synaptic performance in the developing brain.\textsuperscript{218}

Human intervillous blood flow is reported to decrease acutely by 20 percent by smoking a single cigarette, however it returns to normal soon after smoking is stopped.\textsuperscript{201}

1.3.4 Exercise

Placental volumes are significantly greater in women who maintain regular exercise throughout the 2nd trimester. By delivery the increased size is maintained in those who decrease their exercise, but an increase in exercise during the second half of pregnancy is reported to reduce both placental size and birthweight.\textsuperscript{54} This may be due to the fact that exercise during pregnancy decreases uterine blood flow (in animal models) in direct relationship to the intensity of exercise, probably by redistribution of cardiac output.

1.3.5 Summary

In summary the placenta is the main unit controlling the flow of nutrients and waste products to and from the fetus respectively. The placenta alters its function in different ways depending on the type of insult that may cause a disturbance in its normal function. For example the response of the placenta to smoking is to compensate by increasing its own uptake of oxygen hence restricting that available to the fetus.

The factors affecting placental growth is poorly understood, especially in relation to the human placenta. There are a large numbers of factors that affect birthweight, however their effect on placental weight remains uninvestigated. Furthermore there is a relative lack of understanding of the mechanisms by which the placenta reacts to situations and the onflow of these effects to the developing fetus.
1.4 Relations Between Placental Weight, Birthweight and Disease in Adult Life

1.4.1 Background

Birthweight and placental weight are known to be correlated. In general, the correlation between them is approximately 0.5. Over recent years there has been a developing hypothesis relating growth in utero to disease in adult life, in particular cardiovascular disease and non-insulin dependent diabetes. The great majority of this work has come from the MRC Environmental Epidemiology Unit in Southampton, England, the theory more commonly becoming known as "The Barker Hypothesis". This section summarises the work carried out by Barker and colleagues, alongside supporting and dissenting evidence from other groups.

In England and Wales death rates during the past hundred years had been higher in the north and the west of the country. In the past this had been due to differences in the incidences of infectious diseases, in more recent times it was been accounted for by chronic diseases and more specifically ischaemic heart disease.

In 1986, Barker and Osmond compared infant mortality (deaths per 1000 live births) between 1921 and 1925 to deaths in adults from ischaemic heart disease and other major causes between 1968 and 1978 (using standardised mortality ratios). The correlations they found ranged from high to low, the highest $r=0.73$ for the correlation with ischaemic heart disease. Comparing rates of adult death to neonatal and postneonatal mortality found correlations of 0.69 and 0.68, whilst bronchitis was correlated more to postneonatal mortality $r=0.83$. The correlations with ischaemic heart disease were found to be consistent in both sexes and all age categories. They hypothesised that adverse influences in childhood were associated with poor living standards, and increased susceptibility to other influences, associated with affluence, encountered in later life.

A later more in-depth analysis showed that geographical patterns in mortality from cardiovascular disease and chronic bronchitis were associated with past differences in the intrauterine and early postnatal environments. Stroke was related to neonatal mortality which is believed to be associated to the intrauterine environment. Bronchitis was related to post-neonatal mortality which is thought to be related to the postnatal environment. Finally ischaemic heart disease as previously stated was related to both measures of mortality, hence to both the intrauterine and postnatal environments. 30
1.4.2 Systolic and Diastolic Blood Pressure

Gessner et al reported in 1988 that male Swedish army conscripts who had been growth retarded had a risk of increased diastolic blood pressure in early adult life (28 y.o) in comparison to those who had been AGA. Using data from national cohorts from the years 1946 and 1970, Barker et al found among both cohorts that both systolic and diastolic blood pressures were positively related to pulse rate. They found an inverse relationship between systolic pressure and birthweight which was independent of the confounding effects of smoking and parity, and independently a positive relationship between systolic pressure and current weight. This relationship has also been reported by others. Holland showed that this relationship with birthweight became increasingly positive as weight changed throughout life. Hence, weight gain in childhood was positively associated with blood pressure. These associations remained significant after controlling for father’s social class at ages 4 and 36 years, alcohol, and region. In women high BMI at age 36 was associated with high blood pressure. However, low birthweight was not, even though the same inverse relationship was seen. The risk of high adult blood pressure was greater for overweight adults than LBW infants.

Barker's study has shown the inverse relationship reported above was not due to shortened gestation, and therefore may be related to reduced fetal growth. His group has hypothesised that pressure in fetal circulation might be raised as a means of maintaining placental perfusion, which may persist after birth, or that IUGR may lead to accelerated postnatal growth accompanied by an accelerated increase in blood pressure.

These findings have been expanded and show that at all ages beyond infancy, people who had lower birthweight have higher systolic pressures, and that systolic pressure is not related to growth during infancy, independent of birthweight. The relationship between systolic pressure and birthweight, however, becomes larger with age. Relationships with diastolic pressure were shown to be similar but weaker.

In contrast to these results are a number of studies from the UK and overseas. A study in New Zealand found that changes in systolic and diastolic pressures at seven years of age between normal infants and those who had experienced intrauterine growth delay were small and non-significant. A further analysis at 18 years of age found less pronounced effects. Similar results have been reported in Israel and Wales.

In Israel, amongst 17 year olds, systolic and diastolic blood pressures were correlated with body weight, height, BMI, and birthweight for both sexes. Controlling for all factors at the same time however found no
consistent relationship between blood pressure and birthweight. In Wales a study found in a matched study that systolic pressures at a mean age of 15.7 years were not significantly different.

Campbell and Cook have found no relationship between birthweight and blood pressure.

People who had lower birth weight are also reported to be shorter at birth or have small head or abdominal circumferences. These trends are present in both males and females and become stronger after controlling for current BMI, alcohol and gestation. Gruenweld has previously reported a relationship between systolic blood pressure and thinness at birth, however Martyn found no significant association.

Whincup in a cross sectional study of 5-7 year olds found only positive associations of current weight to birthweight, current systolic pressure and current diastolic pressure. There was no significant relationship between birthweight and blood pressure. However, after taking current weight into account, blood pressure was inversely associated to birthweight within quintiles, for both sexes, both before and after controlling for a number of confounding variables including age, infant feeding (which showed no differences) and parity. In comparison to the effect of current weight, the relationships with birthweight are small. A study in Croatia found similar results with systolic pressure, however no relationships were found for diastolic pressure.

A follow-up of these children at age 9-11 found an inverse relationship between birthweight and both systolic and diastolic pressures after adjustment for age, sex, height, and BMI. These relationships were similar in both boys and girls and in term and preterm infants, and were independent of parity, social class, maternal blood pressure and maternal smoking in pregnancy. Compared to when the children were 5-7, the strength in the relationship with systolic pressure was increased, however this was not the case for diastolic pressure.

Godfrey et al have also reported increasing systolic pressure with fingerprint patterns, blood pressure increasing with the number of whorl patterns, and also with an increasing ridge count. Blood pressure was greater if the whorls were on the fingers of the right hand, similarly the relationship between systolic pressure and ridge count was found to be strongest with the ridge count on the right hand. The length of the palm was also found to be associated with an increase in systolic pressure independent of adult height, while the increasing palmar angle was associated with decreasing systolic pressure. The relationships between number of whorls, ridge count, palmar angle and diastolic pressure on the right hand were similar to those for systolic pressure. However, no relationships were found between dermatoglyphics and birthweight, placental weight, length or head circumference.
They hypothesised that the results may be explained by the fact that the whorl formation may reflect fingertip oedema as a direct result of higher fetal blood pressure in early pregnancy. They also hypothesised that the higher incidence of whorls on the right hand could be explained by the anatomical differences in the origins of the right and left subclavian arteries in early gestation. Because the shape of the palm is not related to adult height, they believe this is hence established in utero, and that the relation between palmar angle and large head size may reflect adverse influences in late gestation.88

Subjects that were thin at birth and had placentae below the median placental weight were found to have more whorls and a higher ridge count. Those who were short at birth in relation to head size and had placental weights above the median tended to have narrower palmar angles.88

Barker et al have also reported that in both men and women the highest blood pressures at 46-55 years of age occurred in those who were not only small babies but had had large placentae24. Campbell has also reported this relationship.49 These relationships were independent of each other and controlling for BMI, alcohol, sex and gestation had little effect.24 Whincup found similar relationships after taking height and BMI into account, however the relationship was not significant after controlling for birthweight.244 Martyn et al found no association between systolic pressure and placental weight 145

A further study found similar results among a group of children aged 4, however the relationship was not as strong, the major effect being in the group of children who were heaviest at 4 years. The relationship remained after controlling for ponderal index at birth, mothers systolic pressure and haemoglobin during pregnancy, all of which were associated with systolic pressure. The relations to diastolic pressure were similar but the mean differences were smaller and did not reach statistical significance.131

Campbell et al, in a study on nutritional intake among primiparous women, found that no individual nutrient from the maternal diet was related to birthweight, however a high percentage calorie intake from protein was associated with decreased birthweight.49

1.4.3 Non-insulin Dependant Diabetes, Plasma Fibrinogen etc

Barker et al have reported among one sample of men aged 59-70, that plasma fibrinogen increased with age, however plasma factor VII showed no change. Both were associated with an increasing weight at age one and this was the only association that remained significant after simultaneous regression with height, and birthweight.26 However, another sample found that fibrinogen concentration was not related to birthweight,
however simultaneously controlling for placental weight showed fibrinogen fell with increasing birthweight and rose with increasing placental weight. Martyn has reported that plasma fibrinogen concentrations are related to obesity measured by BMI or waist to hip ratios. Males were also found to have lower levels than females. Among males, plasma fibrinogen levels fell as birthweight and abdominal circumference increased however these relationships were not found in women. Fibrinogen levels were also found to rise as length decreased.

Martyn found no relationships between plasma concentrations of factor VII and any birth measurement. Because males grow faster than females it is hypothesised that they are more susceptible to the effects of nutrient deprivation in late gestation. Another reason may be that effects in women at this age may be transiently obscured due to increases in fibrinogen and factor VII that occur during menopause.

A more in-depth study amongst a subgroup of the above sample found that those with impaired glucose tolerances had been lighter at birth and one year, but were now heavier and had higher BMI's than those that did not have impaired tolerances. Plasma glucose concentrations at 30 and 120 minutes fell with increasing birthweight and with weight at one year. These trends were all independent of current body mass. They suggested that poor nutrition at critical periods of fetal and infant life may lead to impaired development of beta cell function.

Fall et al have reported that, amongst women, fasting plasma concentrations of glucose, insulin, 32-33 split proinsulin, systolic blood pressure, waist:hip ratio and serum triglyceride concentrations fell with increasing birthweight after controlling for current BMI, while serum high density lipoprotein cholesterol concentrations rose. Glucose and insulin levels 2 hours after oral glucose loads showed similar trends. The least favourable outcomes are found for those women who were obese in adult life and had lower birthweights. These results contrast to some extent to those found in men, where fasting glucose and insulin levels were not related to birthweight and low growth rates in infancy were not linked to coronary heart disease.

Looking at a group of children in Pune, India, Yajnik et al have found that, among children with low birthweights, at four years they had higher plasma glucose and insulin concentrations 30 minutes after a glucose load, independent of their current size, compared to a sample of non low birth weight (>2000g) infants.

Cook et al have reported correlation between beta cell function and birthweight in both non-insulin diabetic subjects and non-diabetic subjects. Small for dates infants have fewer beta cells and non-insulin diabetes is
known to be associated with a moderate reduction in beta cells. This is consistent with the hypothesis of Hales et al, however an alternative is that reduced birthweight is associated a beta cell defect with reduced fetal insulin secretion and reduced anabolic activity in utero. They hypothesise that additional genetic or environmental factors leading to more severely impaired beta cell function are likely to be necessary for the development of non-insulin dependant diabetes.

A Danish study comparing a group of offspring of diabetic patients to a group of offspring of non-diabetic subjects found no significant difference in the birthweights of the groups, hence the two groups were combined for further analysis. After combining the groups they found no relationship between birthweight and blood pressure. Birthweight was however found to have an inverse relationship to fasting blood glucose after adjusting for age, BMI, gender of the offspring, and gender and NIDDM status of the parent. They conclude that as birthweight contributes little to the explained variance of cardiovascular disease this does not support the hypothesis of LBW being a major risk factor for hypertension and cardiovascular disease.

### 1.4.4 Cholesterol

Fall et al found that standardised mortality ratios fell with increasing weight at one year of age irrespective of the way in which the infant was fed. However men who had been breastfed and not weaned by 1 year had mortality ratios that rose with increasing birthweight. Serum cholesterol was found to be higher in those who were breastfed but not weaned by 1 year and those exclusively bottlefed compared to other feeding groups. These cholesterol measures included total cholesterol, low density lipoprotein cholesterol (LDL) and ratios of LDL to high density lipoprotein cholesterol (HDL).

Barker at al reported that men and women who had had low birthweights tended to have raised concentration of total and LDL cholesterol and apolipoprotein B. These concentrations were also found to decrease as abdominal circumference increased, the significance of these trends increased after controlling for gestation, and smoking. Trends with these concentrations and length, head and chest circumferences were rendered insignificant after controlling for abdominal circumference. They suggest that in late gestation the fetus may respond to nutrient deprivation by maintaining the brain at the expense of the trunk. The liver specifically, which is growing rapidly at this time, may be particularly compromised. The liver is thought to be the main site for synthesis of LDL cholesterol in late gestation.
1.4.5 Summary

Barker's group has suggested that the associations between birthweight and blood pressure point to a mechanism by which high blood pressure is initiated in utero rather than during infancy and is amplified throughout life. However, others suggest that since the major correlation is between blood pressure and current weight, rather than birthweight, there is a major environmental effect on blood pressure during childhood, not during the intrauterine period.

The theory of the Barker group is expanded with the placental data. Their studies found that greater placental weight at any birthweight was associated with a decrease in the ratio of length to head circumference, which is consistent with diversion of blood away from the trunk to the brain, which, in turn, could alter arterial structure.

Furthermore Barker et al have reported that standardised mortality rates from cardiovascular disease fell with increasing head circumference, but there was no relationship with length. Standardised mortality rates fell with increasing ponderal indices. They suggest, therefore, that small head circumference and thinness at birth reflect patterns of fetal growth. The bodily proportions of these infants at birth suggest that the growth reduction began in early pregnancy, and that maternal nutrition may be an important influence.

1.5 Literature Summary

In summary, this chapter has reviewed the published literature in respect to small for gestational age infants. The review has shown that very little work has been done on SGA infants in New Zealand and that it is an area that requires attention.

The review of the international literature was broken down into associated groups of variables, a summary of the review of the literature on these groupings follows.

1) Socio-demographic variables: The literature shows little effect on birthweight of socio-demographic variables. There is evidence that relationships exist between these variables and birthweight at the univariate level, however the effects noted are relatively small and generally disappear after controlling for other variables.
2) Maternal lifestyle factors: The factors reviewed in this section are those which the mother herself makes a personal choice to partake in. The literature continues to show that smoking is the most important factor in relation to detrimental effects on birthweight, and the risks involved are consistent in the literature, with heavy smokers having a greater risk. Marijuana use shows a risk at the univariate level, however this tends to decrease substantially after controlling for other variables, especially tobacco smoking. In conclusion, there may be a small additional risk due to marijuana use. The literature on narcotic use shows large detrimental effects at the univariate level, however no good controlled studies are available to assess what occurs with these risks after controlling for other variables. It seems likely that the effects of narcotic use will remain important, and this issue is likely to become a bigger problem with the increasing usage of these drugs.

Caffeine consumption and alcohol intake consistently show little effect amongst those who take these substances in moderate amounts. The only risks that are seen to be associated with these substances is amongst the heavy users. There is also confounding present between both these factors and smoking, and further work is required to determine what interactions are taking place.

3) Genetic factors: The associations between birthweight and the factors considered under the genetic heading seem reasonably clear cut. Male infants are known to be heavier than female infants and few studies fail to show this. Different ethnic groups around the world have different sized infants, however one point remains of interest in relation to this. That is whether the difference in size amongst different ethnic groups is related to maternal stature, cultural factors or is in some other way genetically based.

Maternal height and weight show similar and consistent patterns with shorter and lighter mother's giving birth to smaller babies. As one would expect the taller and heavier mother's give birth to larger babies, however the effects for the taller and heavier mother's tend not to be as large as that seen amongst the lighter and shorter mothers, especially after controlling for other confounders.

4) Obstetric factors: Of the large number of obstetric factors considered, several stand out as having more importance than the others. Maternal age shows little effect, however its relationship with parity is likely to be of importance and the interaction between these variables needs further study. Further to the importance of parity is the effect due to grand multiparae, the results of which are still unclear.
Of the remaining variables the ones of most interest and where further research is required are those variables pertaining to previous pregnancies and the effects due to previous small or preterm infants, and previous bad outcomes (including spontaneous abortions, induced abortions, and infant deaths).

5) Nutritional factors and exercise: The literature on nutrition and exercise during pregnancy is relatively limited. Nutrition both before and during pregnancy is of obvious importance to the fetus, however the importance of timing of nutrition is not well studied, especially in the human. Similarly the effects of exercise due to either leisure or employment have not been extensively studied and the effects on the fetus are relatively unknown in the human.

These two areas are rapidly evolving and are recognised as important in the development of the fetus, however is should be recognised that the study of these factors will not be easy due to their interactions and the difficulty in measurement.

The first part of the remainder of the chapter is devoted to the relationships between the placenta and the fetus and the interaction between them during pregnancy. Whilst the placenta is important for a number of reasons, including transfer of nutrients to the developing fetus and transfer of waste products from the fetus, the understanding of the relationship between the two remains poorly understood.

The final section of the chapter describes ongoing work that hypothesises a link between birthweight, (and other birth measurements including placental weight, head circumference and length) and disease in adult life. These links focus mainly on coronary heart disease and non-insulin dependent diabetes. The hypothesis does however show conflicting results from various studies and also has its critics. Much more work is clearly needed in this area if the links between what occurs in utero and disease in adult life are to be proved conclusively.
Chapter 2: Small for gestational age definitions

2.1 Previous and other definitions

Low birthweight (LBW) is defined by the World Health Organisation (WHO) and International Classification of Disease codes (ICD-9) as a birthweight less than 2500g. Low birthweight can result from a short gestation (pre-term birth), intrauterine growth retardation (IUGR), or a combination of both. IUGR and small for gestational age (SGA) are used synonymously, however IUGR infants are classified into categories; those that are symmetrically growth retarded and those who are asymmetrically growth retarded.

The initial problem when dealing with data related to small for gestational age babies (SGA), is the definition of SGA.

Ponderal index = \frac{\text{birthweight}}{(\text{crown - heel length})^3}

Although SGA and IUGR infants overlap to some extent, they are in fact separate issues as SGA infants are not necessarily growth retarded. An infant that is below the 10th percentile for gestational age with a normal ponderal index, would be considered to be symmetrically growth retarded (in that all body measurements would be proportionally smaller). Such an infant though may not necessarily be growth retarded and may simply be small due to genetic potential, (especially in the case of small maternal stature). Kramer et al showed in 1989 that lighter infants became more disproportionate, from normal to low birthweight, in that the lighter infants had larger ponderal indices. This work has been extended in New Zealand by Hofman & Cutfield to severe IUGR infants (unpublished).

SGA is preferred in this work over IUGR since SGA describes the infants and makes no judgement on whether they have growth retardation or not.

American and UK definitions of birthweight percentiles are often used to define SGA but are not necessarily appropriate to the New Zealand population. It assumes that NZ babies are distributed with the same birthweights as US or UK babies, which is unlikely to be true, because of the different ethnic and social mix of the populations.

As the definition of SGA is dependent upon birthweight for gestational age percentile charts, the choice of charts and specificity to certain factors is crucial. Four factors that need to be considered are 1) Sex, 2) Ethnicity, 3) Country of origin, and 4) Parity:

1) Sex: It is commonly known that male infants are heavier than their female counterparts at any given gestational age. Thus, it is appropriate that percentile charts should be sex specific, otherwise a much larger proportion of female infants would be classified as SGA, a number of them inappropriately, and few male infants would be classified as SGA. Kramer\(^{120}\) found a difference of 126.4g in the mean birthweights of males and females in developed countries. In the dataset of all births in New Zealand for 1990 and 1991 (which will be used to define percentile curves) male infants were on average 112.5g heavier than female infants.

2) Ethnicity: Ethnic differences are not as straight forward as the difference between male and female infants. The issue relates to whether or not differences in birthweight in different ethnic groups are due to genetic factors. In some ethnic populations (for example the Pygmies of equatorial Africa who are diminutive in size)
this is an important consideration due to the obvious discrepancies in body structure. However, in New Zealand it is not so obvious a factor.

In New Zealand, ethnic minorities are still a small percentage in comparison to the general European population. The main ethnic groups in New Zealand using a biological basis for definition as used by Statistics NZ in 1993 are Maori (9.7%), Pacific Islanders (3.8%) and European (79.5%) the rest of the population is made up of smaller minority ethnic groups (such as Indian and Asian) and mixed ethnicities, using current Department of Statistics definitions for ethnicity. Only a small proportion of births are Asian at the present time although the number is increasing. Maori babies tend to be slightly smaller and Pacific Island babies slightly heavier than European babies.

Furthermore, the relatively few births in New Zealand per year within ethnic minority groups would make race specific curves extremely unstable at the shorter gestational ages. Use of a greater number of year’s data, may be inappropriate due to changes in birthweight that may be occurring over time.

In New Zealand the previous published percentile curves are those of Buckfield et al based on singleton European births at Queen Mary Hospital in Dunedin during 1967-1973 and 1975-1978. Although these percentile charts are sex specific they only include NZ European births. They also excluded an unknown number of subjects since the exclusion criteria included an unsure date of last menstrual period, and the presence of disorders known to affect fetal growth. In addition the number of subjects was very limited, especially at the shorter gestational ages, (the smallest being 5 female subjects at 31 weeks gestation). Furthermore, infants born in Dunedin are not necessarily representative of infants delivered throughout New Zealand. The percentiles were also derived from births up to 25 years ago and it is likely that birthweights have changed over time in NZ as they have in Canada. All of this is likely to make Buckfield’s percentiles of little use for present day standards.

3) Country of birth: The difference in birthweights of infants born to women who were not born in New Zealand is unlikely to affect the percentile curves much in the New Zealand population at this time, due to the small proportions of infants from ethnic groups with significantly different birthweight percentile distributions. Other countries have however reported differences in subsequent generations of immigrant mothers. Country of origin may be an important factor, though this information is not available on the dataset to be used here, and hence is unable to be used in the calculation of birthweight percentiles. Birthweight percentiles will therefore be for all births registered in New Zealand.
4) Parity: Primiparity is an important factor to consider as primiparous mothers have consistently been shown to deliver smaller infants. In New Zealand, the number of births per year would make parity specific percentiles unstable, especially at the lower gestational ages. Separate percentile curves may be appropriate for primiparous and non-primiparous mothers, however complications would then arise in both producing and using the percentile curves in relation to mothers who had previously had an abortion, miscarriage and other such outcomes. Like country of birth, parity is also unavailable and parity specific percentiles unable to be produced.

It was therefore decided to use available data to establish sex specific birthweight percentiles by gestational age for NZ.

2.2 Methods for current percentile definitions

Data was obtained for all registered live births occurring in New Zealand in 1990 (n=58639) and 1991 (n=58458). Gestation was reported in completed weeks and birthweights in multiples of 10g. Tables 2.1 and 2.2 show for each gestational age the frequency (i.e. the number of pregnancies), mean birthweights and standard deviations for male and female infants respectively.

Firstly, birthweights were plotted by sex and gestation for males (fig 2.1a) and females (fig 2.1b). As can be seen from this plot, there is an anomaly in the data at 30 completed weeks gestation, in that whilst the data at other gestations is seemingly normally distributed, that at 30 weeks gestation is skewed. The data at 30 weeks has a much greater number of outliers on the heavy side, occurring in both years of the data set and for both sexes. This anomaly was investigated through the source of the data (Department of Statistics) who verified that the data had been entered correctly from the data sheets and checked against hospital records. However, it seems unlikely that this is a true effect as the birthweights seem improbable for the given gestation, hence it seems that wrong gestations and/or birthweights have been recorded. A most probable explanation seems to be an error in the typing of 36, 38 and 40 weeks gestation transcribed as 30.

The data problem explained above led to a small number of extreme outliers at 30 weeks gestation (infants >2400g) being removed from the dataset (37 observations). Data points less than 24 weeks and greater than 44 weeks completed gestation (56 observations) were also removed as there was not enough data available at these ages to produce stable centiles.
Medians, Lower Quartiles (LQ), Upper Quartiles (UQ) and Inter Quartile ranges (IQR) were then determined for each gestational age. Any data points that were identified as being greater than 2 inter-quartile ranges below or above the lower and upper quartiles respectively, were classified as outliers and removed from any further analysis of the percentiles. Whilst this technique would have removed a number of the extreme outliers at 30 weeks, (because there were so many of them at a relatively uncommon gestational age), it would have markedly affected the median and quartiles and hence a number would have remained in the sample. Hence the previous deletion of these physically improbable observations.

Anthropometric data may be skewed. The skewness of such data can often be removed by the process of using a power transformation to smooth the data. This will shrink one tail of the data and stretch the other. This fact has been used by Cole in deriving a method that obtains normality for a series of age groups, which then allows centile curves to be drawn. This data was normalised for gestational age using the groupings of 24-26, 27-28, 29-30, 43-44 weeks and the other gestational ages (31-42 weeks) in unique weekly groups. Grouping of these less common gestational age groups is valid and was needed due to this method requiring a minimum of approximately 100 observations in a group in order to normalise the data appropriately.

The effects of applying this technique were only small. In the majority of cases, the data was so near normally distributed that raw percentiles at any gestational age were only affected by approximately 10 grams.

This data was then used to determine the 3rd, 10th, 50th (Median), 90th and 97th percentiles for gestational age for each sex.

Given the general cubic nature of birthweight percentiles, models were fitted to the medians that included a linear, squared and a cubic term, all terms in the model were statistically significant (p<0.0001). Examination of the predicted values from these models detected values that were not as near the observed points as one would desire. It was therefore decided to add a quartic term to the model. Doing this improved the fit of the models, the residuals were smaller and all terms in the models remained significant (p<0.05). Models including these four terms were then fitted to the 3rd, 10th, 90th and 97th percentiles. The four terms in the model fitted the percentile curves well, with no major discrepancies in the size of the residuals.

The method described above allowed the data points to be fitted closely. It would not however be appropriate to use the equations derived for these curves outside of the gestational range for which the
curves are drawn. This is due to the fact that the gradient of the curve, which indicates the rate of growth, is continually changing. Above 44 weeks and especially below 24 weeks the growth patterns may be quite different. Patterns of growth below 24 weeks may be able to be determined using ultra-sounds and other methods, but these methods may be unreliable in measuring the weight of the foetus.

2.3 Results of the National percentile curves

The techniques described in the above section produced models for the curves (figs 2.2a and 2.2b), the equations for these percentile curves are shown in table 2.3. These models were then used to calculate points for birthweight to determine the percentiles at each number of weeks gestation for both male and female infants. These weights were rounded to the nearest 10g and are shown in Tables 2.4 and 2.5.

Comparison of the curves for male infants and female infants (fig 2.3) show the pattern that was expected (with male birthweights being higher than those for their female counterparts at the same gestational age). It is interesting to note, however, that the difference between the curves is not constant and increases as gestational age increases. The absolute difference and percentage difference of the raw and fitted 50th percentiles (medians) can be seen in Table 2.6. The raw data showed some unusual fluctuations especially notable at 24 and 29 weeks gestation. After the removal of outliers and the normalising of the data, even though the difference in the absolute percentiles becomes larger, the percentage by which males are larger than females is relatively constant. This suggests that the increasing absolute difference with age is a function of increasing absolute weight and not of biological significance.

It has also been suggested that birthweights are changing over a period of time. Although the data for New Zealand previously is limited to that published by Buckfield (which has a number of weaknesses as previously described), it is probable they are reasonably correct for mid-percentiles around term gestations.

A comparison was made in both sexes to see if there were any indications that the percentile curves have moved over time. The 10th, 50th and 90th percentiles were compared as these give an idea at the upper and lower end of the scale as well as that shown by the medians (50th percentile).

In the female infant curves (fig 2.4b), the median weight of babies have increased for those babies of 39 or more weeks completed gestation. Below this number of weeks gestation, they are at a similar level. The 10th percentile is also higher from 39 weeks completed gestation and at a very similar level down to approximately 31 weeks gestation. Below 31 weeks the 10th percentile is lower than that previously observed. The 90th
percentile is higher below 33 weeks and above 39 weeks than previously observed, whilst the two curves are at a similar level between 33 and 39 weeks gestation.

The male infant curves (fig 2.4a) show a similar pattern for those infants from 39-40 weeks gestation up, in that they are heavier than those previously reported by Buckfield et al 43. For gestational ages below this, the 10th and 50th percentile curves remain very similar. However, the 90th percentile curve is similar down to 35 weeks gestation, and then below 35 weeks the curve for 1990-91 runs at a higher level. Again this is likely to be due to the instability of the curves at these lower gestations.

There may be a number of reasons for the differences in the curves at the lower gestations: a) The previous percentile curves are very unstable at the lower gestations due to extremely small numbers of observations. b) Possibly more infants are electively delivered early when the prognosis from being preterm is considered to be better than remaining in-utero, which may be especially true for the 10th percentile curve. c) The Buckfield curves are more linear, the higher order term in these models giving the percentile curves more shape towards the extremes.

This perhaps indicates that babies born today are on a whole, heavier than those of 15 to 25 years ago. This may be due to better nutrition, antenatal care and other such factors that will be investigated later.

The difference in the shape of the National and Buckfield percentile curves is unlikely to be due to the use of models with different degrees of higher order terms. The Buckfield curves as drawn here are simply points as defined by the authors with straight lines drawn between consecutive points. Unfortunately further information on the curves that were fitted is unavailable due to the death of the primary author. The National percentile curves are models as described in the text, the curves fitted to the defined percentile points.

Drawing lines between the consecutive points may have a minimal effect on the shape of actual curve between consecutive points for the Buckfield curves. The degree of model fitted to these percentiles will not however greatly affect the shape of the curves between points, especially in the middle gestations, though may affect the shape at the early and late gestations.

The place where the curve's shape would differ most is outside the range of gestational ages for which the percentiles are actually defined. This is however of no concern as the percentiles are not compared outside the gestations shown and were not defined in the Buckfield percentiles.
The preterm rate (<37 weeks completed gestation) from the 1990 and 1991 data was 4.7%. This was slightly higher than that in the data of Buckfield et al (3.8%) (P. Herbison, personal communication). This rate is low compared with other regions (Canada 6.2%, North East Thames (London, England) 7.0% (L. Hilder, personal communication).

This chapter has described the definition of the outcome of interest (SGA) and its relationship to terms often used synonymously with it, along with reasons for using this definition. Updated sex-specific birthweight percentiles have been defined to enable the study of this outcome in the New Zealand population. Comparisons have also been made between the male and female percentiles, and between these and the previously defined NZ percentile curves of Buckfield in looking for differences between sexes and over time respectively. These comparisons show differences in sexes, hence the need for sex-specific percentiles, and probable increases in birthweight over time, suggesting that birthweight for gestational percentiles need updating every 5-10 years.
Chapter 3: Study Designs and Datasets

The outcome of SGA (the binary outcome) and birthweight (continuously) in this thesis is investigated with two datasets. The first is a sample of infants representative of the New Zealand population. The second is a population of all births from the major obstetric hospital in the Auckland region.

3.1 The National Study (New Zealand Cot Death Study)

3.1.1 Study Design

The national cot death study controls comprised a sample of 1800 infants that were randomly selected hospital births from an area that covered 78% of all births in New Zealand during the study period (1 November 1987 to 31 October 1990). Areas included in the sample were the health districts defined at the time: Takapuna (1988 boundaries), Auckland (1988), South Auckland (1988), Hamilton (1988), Rotorua (1988), Napier (1985), Hutt (1988), Wellington (1988), Christchurch (1988), Dunedin (1985) and Invercargill (1985).

The data was originally collected as the control sample in the New Zealand Cot Death Study (NZCDS). The sample was selected with respect to some factors as will be described below, namely; age of infant, hospital, and day of the week. These factors were not related to the outcome of interest in this thesis since birthweight of the infant was determined before the subjects were selected for the NZCDS.

The subjects were randomly selected from all births, with the exception of home births, which at the time comprised less than 1% of all births in the participating areas.

The subject selection process for control subjects was determined by the following:

a) A date for interview (nominated date) was randomly selected from all 365 days.

b) The control was then randomly allocated an age at which to be interviewed to ensure that the control group had a similar age distribution to that previously described for cases. (The age distribution was
calculated from national data from 1979 to 1984 supplied by the National Health Statistical Services (NHSS)).

c) The date of birth was calculated from age and date at interview.

d) Births by day of the week vary considerably, due to the induction of labour. The day of birth was adjusted to fit the expected distribution by randomly choosing days of the week in a) in proportion to the number of births on days of the week from the previous financial year.

(e) An obstetric hospital was randomly chosen in proportion to the number of births over the previous financial year.

(f) In hospitals with more than one birth on the selected day, random numbers were used to select a particular infant from among those born on the nominated date. For obstetric hospitals where there were no deliveries on the nominated day, a randomly allocated direction indicator was used to indicate whether to go forwards or backwards in time to select the infant.

Points b) and c) have no effect in this thesis since they do not have any effect on the point in time in which the interest of this work lies (i.e. birth). The other points ensure a random selection of all births in the study areas.

The data used here was collected from two sources. The first of these was a retrospective interview of one or both parents of the infant. This interview was mainly aimed at collecting information on infant care practices but also collected information on infant outcomes (e.g. gestation and birthweight) and maternal obstetric history. The second source of information was the obstetric records which is prospectively recorded information, containing obstetric history, and maternal characteristics as well as infant information.

This sample in effect forms a cross-sectional study.

### 3.1.2 Sample Size and Availability

From the sample of 1800 infants, 1592 (88.4%) subjects completed the interview part of the study, and obstetric information was able to be collected on 1762 (97.9%) infants. Birthweight and gestation was available for 1761 infants. Of these 1761 infants, 85 (4.8%) were preterm (<37 weeks completed gestation) and were eliminated from the analysis, so that any effects found would be related to SGA and not preterm
birth. Of the remaining infants, 157 (9.4%) were below the 10th percentile as defined in chapter 2. Of the 1676 term infants, 1513 (90.3%) completed the interview (143 (91.1%) of SGA cases and 1370 (90.2%) of SGA controls), and the obstetric records were obtained for 1667 (99.5%) (155 (98.7 cases and 1512 (99.5% of controls).

The mean birthweight and gestation of the group of infants for whom an interview was carried out, were 3490g (s.d.=502g) and 39.8 weeks (s.d.=1.16) respectively. The mean birthweight and gestation of the infants for which no interview was carried out was 3464g (s.d.=477g) and 39.8 weeks (s.d.=1.28). Hence, there were no differences in mean birthweights or gestation for the two groups. Those interviewed were considered representative of the whole sample as far as the outcome of interest here is concerned.

3.1.3 Factors to be Examined

As mentioned, the data used in this sample was collected from two sources, the first and main source of information was a retrospective interview with the infant’s parents. This interview was mainly aimed at collecting information on infant care practices but also included questions relating to:

i) Maternal demography: including; age mother left school, socio-economic status (defined using the higher of the parent’s occupations which were then classified using Elley Irving scales for socio-economic class.70), marital status, and maternal social support (a recognised scale for measuring maternal social support.177).

ii) Obstetric history: including; maternal age, parity, antenatal care, and urinary tract infection.

iii) Genetic factors: including; ethnicity (i.e. infants ethnicity defined by parents on cultural grounds), maternal height, and pre-pregnancy weight.

iv) Maternal life style: including; tobacco smoking, marijuana use, alcohol and caffeine consumption.

Information was also obtained from obstetric records, for the purpose of obtaining infant measurements and maternal obstetric history.
3.2 Hospital Based Data

3.2.1 Study Design

The other data used in this thesis is from a hospital based dataset. This dataset contains all births that occurred at National Womens Hospital (NWH) during the calendar year of 1992.

Data is collected on all women that deliver at NWH. Most of these women have had their antenatal care carried out at NWH, though a small proportion turn up for delivery with no prior association with the hospital. Some women are transferred in from other hospitals with problems, since NWH was, at this time, the only level 3 neonatal unit in the Auckland area. For the purpose of having a definable population, all transfers in from other hospitals have been removed from the dataset as they are likely to be different from those that were booked at NWH.

Information is collected at antenatal booking and at antenatal checkups throughout pregnancy and entered into the hospital database. In addition, data relating to the birth and the infant is entered post delivery.

This sample is a definable cohort of women for study and for whom results can be extended to similar populations.

3.2.2 Sample Size and Availability

The data used is from a database (Auckland Maternity Services Information System (AMSIS)) that currently runs at National Womens Hospital, containing information on approximately 8,000 deliveries a year, representing approximately one seventh of all deliveries in New Zealand and half of all the deliveries in Auckland.

With such a large population, SGA was able to be considered from both the point of view of the 3rd and 10th percentiles for gestational age.

In 1992 there were 8696 infants for which data was recorded, of these 786 (9.0%) were transfers from other hospitals either antenatally or postnatally. The remaining 7910 were deliveries at NWH, of which 683 (8.6%)
were preterm, leaving 7227 term infants (>=37 weeks completed gestation). These 7227 term infants comprised 168 (2.3%) below the 3rd percentile, 413 (5.7%) between the 3rd and 10th percentile, and 6646 (92.0%) equal to or above the 10th percentile for gestational age.

A certain amount of data is missing for a number of patients. The basic information of maternal demography is available for nearly all pregnancies, however women whose care was carried out through a private obstetrician often have other data missing. This unfortunately limits the analysis as far as SGA is concerned. It is difficult to know how this missing information will affect the results of analyses. With the bulk of missing data on some variables due to private patients, the sample may not be entirely representative for some variables.

Another outcome of interest is the relationship of birthweight to placental weight. This dataset also contains information on birth outcomes, including birthweight, placental weight, crown-heel length and head-circumference. This data was available on 6436 (89.1%) of the term infants.

The issue of infants with large placentae will be discussed in more detail later in this thesis since it has not been described previously and the definition of these infants needs to be considered more carefully.

3.2.3 Factors to be Examined

The NWH dataset contains some, but not all, of the variables available on the national (NZCDS) dataset. These variables will enable comparisons to be made in relation to the consistency of results between the two datasets. Such variables include; marital status, maternal education, maternal age, parity, antenatal care, ethnicity, maternal height and pre-pregnancy weight, and smoking. Variables included on the NWH dataset which were not recorded in the NZCDS dataset or not collected are; booking trimester, geographical area, paternal age, paternal education, previous caesarean section, blood pressure (maximum diastolic), previous miscarriages, induced abortions and previous low birthweight infants (<2500g), antenatal ward admission, and maternal haemoglobin (lowest antenatal), and number of ultrasound examinations.

As mentioned previously a number of variables had large amounts of information missing, which allowed for some of these variables to be examined only at the univariate level, since inclusion in the multivariate analysis would have excluded a large number of observations.
3.3 Study Biases

A number of biases may be present in both datasets under investigation. Those of concern and most likely to be present in these datasets are selection bias and recall bias.

Selection bias may be present if the sample of subjects who take part in a study are not representative of the population from which they were chosen. This may occur because a subsample of those chosen may elect not to take part. For example, if in a study on birthweight, mothers of all the smallest babies chose not to take part, then the risks estimated by the study may be biased because of a differing prevalence of risk factors amongst the mothers of these smallest babies.

Recall bias may occur in retrospective studies when subjects belonging to a group, perceived to be the bad outcome, are more likely to recall events that they feel may have had an influence on that outcome. For example, if a group of mothers of babies who had died were asked whether the baby had a runny nose in the last two weeks, it may be more likely for these mothers to recall this event over mothers whose babies were still alive and well. This would result in the two groups recalling an event with differing amounts of misclassification, and would result in a bias in the measurement of risk. This type of recall bias is known as differential.

Recall bias can also occur when two groups report an event with the same amount of imprecision. This leads to a bias in the prevalence of the event but does not effect the measurement of level of risk experienced by one group over the other. This is known as non-differential recall bias.

3.3.1 National Study

The study design of the national study is such that selected infants are a representative sample of all infants born in the areas covered by the study. Because the response rate was 90.3%, for the most incomplete part of the data collection, it is unlikely that any selection bias is present. The only possibility being that those who refused to be interviewed for this study, or could not be found, may differ in some way from those who did take part. This is unlikely however since birthweights and gestations did not differ between the two groups.

Because the study was, a) not designed to research SGA specifically, and b) a representative sample of all births in the regions they are chosen from in New Zealand, the possibility of recall bias is unlikely. Any recall
bias that may exist is likely to be non-differential and hence the results will not be affected. This will help in the implications and generalisability of results that the investigation shows.

3.3.1 National Womens Hospital Study

Selection bias is unlikely to exist in the National Womens Hospital study as the subjects used in this study are a defined population.

The information on the cohort from NWH is routinely collected information and hence no biases should be present. The lack of information on some variables may cause bias in the results, although it is unlikely since these variables are not used in the multivariate analysis. This could however lead to biased estimates due to the lack of control of confounding.

The more specific problem with NWH study is that the hospital accepts transfers of high risk pregnancies from other hospitals. This will bias the results if factors amongst these transferred pregnancies differ from those of the non-transferred pregnancies. This problem has been minimised in these analyses due to the fact that as previously stated; "For the purpose of having a definable population, all transfers in from other hospitals have been removed from the dataset as they are likely to be different from those that were booked at NWH".
Chapter 4: Methods of Analysis

4.1 Q-Q Plot Interpretation: A Method of Categorising Independent Variables

A Q-Q plot is a method for comparing two distributions. Within this thesis, points are the proportions of cases and controls that have values for the independent variable up to, and equal to, a given value of the independent variable. A gradient above 45 degrees (the gradient represented by the straight diagonal line on the plot indicating a constant odds of one) between points, indicates an increased risk for subjects falling in that category. A gradient below 45 degrees indicates a decreased risk. The use of this method was recently proposed by Wartenberg and Northridge for giving appropriate cutoff points when categorising independent variables.238

Programs were developed using SAS to produce these Q-Q plots. There are three programs run sequentially, since information from the earlier programs is used in the subsequent programs. These programs are shown in Appendix A. The first program subsets the data set into separate case and control datasets and then sorts them by the variable of interest. A calculation of cumulative frequencies is then done for the dataset of the independent variable up to and equal to each value of the independent variable.

The second program starts by taking the last observation from the case and control datasets which contains the cumulative totals for the cases and controls. The rest of the program then takes each cumulative frequency and divides it by the total number of observations so that proportions are produced.

The third and final program writes these proportions to a file and reads them back in to change the data matrix from a 1 observation by n variables to n observations by 1 variable. The next part of the program creates a data set that identifies the points with which to draw the guidelines of the plot. The datasets containing the proportions and points for the guidelines are then merged together and the plot is produced and annotated.

Q-Q plots allow investigation of changes in the gradient, and may help in grouping together consecutive values of the independent variable that are of similar risk, instead of simply using a priori cutoffs for the categorisations. They also allow confirmation of the expected univariate behaviour of a variable in relation to the outcome in question. Q-Q plots can help to determine unexpected or unknown patterns, as well as having the ability to see which categories behave in a similar way at the univariate level.

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If Q-Q plots show what is expected, it is logical to carry on with the use of \textit{a priori} categories having had the \textit{a priori} assumptions confirmed. However, when the behaviour of a variable is not as expected, investigation is needed to understand why the univariate levels of the variable are behaving as such.

\textbf{4.1.1 How Various Types of Variables Should Be Treated}

Calculating odds ratios to estimate the relative risk requires the use of a binary outcome and an independent categorical variable. These independent variables will, in the raw form, take one of three general types: (1) A simple \textit{YES/NO} type variable, (2) variables that are of a \textit{discrete} nature, and (3) variables that are \textit{continuous}.

1. \textbf{A simple \textit{YES/NO} type variable}

A \textit{YES/NO} type is the simplest case as the categories are well defined and no arbitrary decisions have to be made about which subjects should belong in which categories. An example of this type could be in answer to the question "Are you married?". A Q-Q plot will not give any additional information in this situation and will simply be a straight line which shows which group has the increased risk (see Fig 4.1).

2. \textbf{Those that are of a \textit{discrete} nature.}

Variables that are of a discrete nature come in two forms.

\begin{enumerate}
\item \textbf{Nominal variables; are those that do not have any order to them;} for example 'ethnic origin'. This type of variable, as in the \textit{YES/NO} case is of a simplistic nature and therefore no additional information can be gained from a Q-Q plot. Whilst, sometimes, some of the categories can be joined together due to small numbers in some categories or similar odds, this can be done just as easily from univariate odds ratios. This can of course lead to misleading information due to different confounding variables in the groups combined, so such situations should be avoided if at all possible.

\item \textbf{Ordinal variables; are those that have some order to them;} for example 'socio-economic status'. This type of variable has sometimes been created with pre-defined classifications, often for a different purpose. In such a situation, fewer categories may be required or may be suitable for such reasons as; lack of numbers in a particular group, and/or to decrease the degrees of freedom in a model. The question is "Which categories can be amalgamated?".
\end{enumerate}
The categories that can be amalgamated will depend on the outcome variable that we are interested in. Therefore each variable must be placed in the context of this outcome. A *priori* thoughts on the categorisation of independent variables are essential, as one must understand the basic behaviour of a variable in relation to the outcome in order to be able to carry out categorisation out in a sensible manner. Q-Q plots in association with a priori thoughts therefore seem the most sensible approach to categorisation of independent variables. *Let us consider an example of this:* The categories for socio-economic status (SES) go from I (high) to VI (low) and others (VII). The standard *a priori* re-categorisation for socio-economic status is to re-categorise into three groups being high (I,II), middle (III,IV), and low and others (V,VI,VII).

If we make a Q-Q plot of this data with the outcome as SGA (as defined in chapter 2), what we find is a pattern different from that assumed to be the case (Fig 4.2). From the point of SES I which is slightly below the line indicating an odds ratio of 1 (showing SGA cases are less likely to be of SES I than controls), there is a decrease in risk for SES II as the line between these points moves in a downward direction away from the line indicating no change in risk. The line between SES II and III continues at a similar gradient to that between SES I and II. This suggests that SES II and III have similar risks. The line from the point for SES III to SES IV shows a change in direction and gradient. The change in direction indicates an increase in risk for the cases in this category (compared to controls) in relation to those in the first three SES groups. The direction being at a greater angle than the diagonal, also implies an increase in risk over the SES I group. For the remaining groups there is again a change in direction, implying a change in risk. The gradient is similar across these remaining categories indicating a similar risk. The gradient being in a slightly downward direction in comparison to the diagonal implies a slight decrease in risk for SES V, VI and VII over those in SES I.

The most striking feature of this plot is the change in direction and gradient moving from SES III to SES IV. These two groups, as stated previously, would be combined normally in the *a priori* situation to define “middle class”. The use of the Q-Q plot in this instance has not confirmed our *a priori* assumptions but has detected the difference between the SES III and IV groups that form the joint middle SES status.

It should be noted that this analysis is at the univariate level and it is possible that an effect such as this may only exist at this level and not at the multivariate level.
3. Variables that are continuous

Continuous variables are often categorised for the purpose of determining odds ratios, hence increased or decreased risks for a group of individuals. This is due to the fact that it is easier to interpret the difference between defined groups of people than it would be given an increase in risk per unit.

The nature of continuous variables differs widely both in the type of characteristic that is being measured and the relationship across its range to the response variable. There are several types of continuous variables:

i) **Limited Range**: Some continuous variables act almost like the second type of discrete variable. Whilst it is continuous, the range is limited. When using the Q-Q plot technique to categorise such variables, the approach as described for the second type of discrete variable is generally appropriate.

ii) **Continuous with a Linear Relationship to the Outcome**: This means that for each unit increase or decrease in the independent variable, there is a constant change in the response variable. This therefore allows arbitrary cutoffs to be made along the continuous variable. It would be sensible if such cutoffs were evenly spaced along the range of the independent variable for interpretation of odds ratios.

iii) **Continuous with a Non-linear Relationship to the Outcome**: There are also variables where the relationship with the response is of a non-linear form. A good example of this type of relationship is shown by Wartenberg with the quadratic relationship between mother’s age and low birthweight (LBW) (Fig 4.3). This relationship shows an increased risk of LBW for younger mothers and also for older mothers, with the other mothers having the lowest risk of a LBW baby. The main problem with this type of variable, when categorising, is to decide where the change in risk occurs. This is not difficult if the change is large between the two groups, but can however be difficult when the changes between groups are small. The Q-Q plot then is used to determine when the gradient of the curve changes direction, which is then the appropriate place to split the continuous variable.

Such relationships may be quadratic or U shaped, so that the increased risk the same distance either side of some midpoint, which has the lowest risk, is equivalent. Most non-linear relationships tend not to act so nicely though and are more often J shaped, i.e. the increased risks on either side of the low risk group have different gradients and one side will comprise a smaller range. In such circumstances, categorisation is a much nicer and simpler way of modelling the independent variable to the outcome.
iv) **Continuous with a Dose-response Relationship:** For this type of variable there is not usually a constant increase of risk across each unit with an increase in the independent variable. Instead, there may be a dose-response increase. For example a more appropriate method of categorising the question "How many cigarettes do you smoke a day?" usually elicits an answer that tends to be rounded to the nearest five cigarettes (see Chapter 5.4.1). Hence, in this situation it may in fact be misleading to use the variable as a continuous one due to the small numbers of observations at points in between multiples of 5. Use of Q-Q plots is useful in determining where the appropriate changes in dose may be, shown as changes in the gradient of the odds.

v) **Continuous with a Threshold Effect:** Similarly, a variable such as smoking could have a threshold effect. This occurs when either: 1) a certain level of exposure is reached, the risk does not increase any further, or 2) where exposure to a factor is safe to a certain level beyond which it then causes ill effect (e.g., radiation). Q-Q plots are also useful in this type of situation in either showing that there is no further change in the gradient of the risk, or, where the gradient changes to one of risk.

A Q-Q plot for a continuous variable usually requires some rounding to the nearest whole number (half or some other appropriate measure). There is a necessity for each point to include a reasonable number of new observations or points. If not, the points in the Q-Q plot would end up too close together and spurious changes in gradient and direction would begin to show. On the other hand, one does not want too few points in the Q-Q plots either or the important changes in direction or gradient may be missed.

An example of a Q-Q plot using a continuous variable is shown in Figure 4.4, using the variable maternal body mass index (BMI) in relation to SGA. The points on the graph are rounded to the nearest whole number for the measurement. The first point shows an increased proportion of cases to controls. The line to the next point also shows a gradient larger than that of the diagonal. This implies a greater proportion of cases than controls are present in these groups of low BMI, with an increased risk for these individuals of having an SGA infant. There is a small change in gradient to the next point and a larger change in gradient to the following point. The first change still sees the gradient larger than the diagonal. But then in the second change, the gradient is less than that of the diagonal. Therefore the middle point is probably an appropriate point for a category break. Therefore, the category break would include individuals with a BMI up to 19.

After the gradient change, the gradient is relatively constant till the point for 24, and then there is a decrease in gradient to 25, thus suggesting the next category cutoff at <24. Thereafter the numbers of individuals in each unit change becomes smaller as the line descends a little before ascending a bit and descending again.
Here one needs to consider the biological reality. The group with a BMI less than 19 would biologically be thin, and those with a BMI between 19 and 24 would be thought of as normal weight, those with a higher BMI would be obese. Hence biologically it is sensible to group the remaining individuals together instead of trying to define a number of groups with small numbers in them that will not have any biological plausibility.

4.1.2 Criticisms of the Method of Q-Q Plots

The method of Q-Q plots (probability plots) to determine cut-offs has been criticised by Altman on statistical grounds for three reasons. 1) The multiple testing invalidates the p-value associated with the chosen cutpoint. 2) The relative risk for the chosen cutpoint will be biased away from zero. 3) It is not an appropriate way of analysing continuous variables, since it is wasteful of information and leads to the false implications that the risk is constant on either side of the cutpoint. 17

Altman also states that it is possible to adjust p values for multiple testing, but the estimates remain biased and cutpoints should be chosen prior to data analysis, or that continuous variables should be modelled continuously. 17

The authors who proposed the technique of Q-Q plots have stated in reply to Altman’s criticisms that the intent of the method is one of exploratory data analysis. They make the point that in observational epidemiology, few situations of sufficient clarity and knowledge exist to define a priori the optimal exposure cutpoint. Furthermore, arbitrary selection of a specific cutpoint provides no assurance that the correct interpretation of the data is achieved or the full pattern of the results is summarised. 206

Therefore, it is important to understand that Q-Q plots are exploratory statistical displays which depict the distribution of exposure in cases compared to controls. The graphical format enables one to simultaneously see the overall distribution of each value of exposure in the study and the odds ratio resulting from the use of each possible dichotomous classification. In addition, if there are two or more candidate exposure measures, a probability plot facilitates a direct visual evaluation and quantitative comparison of these measures with one another. 206

More specifically the authors of the Q-Q plot method have stated that “Probability plots indicate whether the test results are typical of the data or whether a single cutpoint gives anomalous results.” However, as already stated, probability plots are an exploratory tool and should be viewed more as descriptors than as valid tests of hypothesis. Also, inappropriate choice of a cutpoint leads to
misclassification which reduces the statistical power of the analysis. There is no easy way to assess the adequacy or representativeness of one such cutpoint.

More specifically a response to each of Altman’s criticisms is outlined below:

1) **Multiple testing invalidates the p-value associated with the chosen cutpoint.** One way of selecting a cutpoint is to use the one that has the most impressive effect of the exposure variable on the outcome. Careful interpretation and adjustment are required to qualify the final result. Common methods for adjustment when multiple tests are performed, (like the Bonferroni method), do not fully exploit the dependence between the statistics involved, leading to conservative results. Results are therefore frequently left unadjusted, usually accompanied by a cautionary note that the finding is exploratory.  

2) **Relative risk for the chosen cutpoint is biased away from zero:** The effect of choosing the cutpoint associated with the maximum risk leads one “to be conservative in a public health sense” and only if it “provides a relatively stable estimate”. However, the variability and bias of the risk estimates resulting from optimal fitting of the data, will result in a wide range of cutpoints and risk estimates among otherwise comparable studies. Cutpoints based on prior knowledge are preferable and should at least be included in the analysis in order to retain comparability with other studies. If only a priori cutpoints are used however, clearly some of the information in the data is neglected.

3) **Q-Q plots are not an appropriate way of analysing continuous variables:** From the point of view of constancy of risk on either side of a cutpoint, probability plots can be used to display the sensitivity of the odds ratio to the choice of cutpoint. They can also be used to investigate how risk changes for different levels of the exposure factor. Probability plots should be used as a precursor and adjunct to statistical modelling. Furthermore these plots are useful for the description of complex data sets and for hypothesis generation. On the other hand though, statistical inferences drawn from them are complicated, as Altman pointed out, by problems of multiple comparisons. A particularly useful feature of the probability plot, however, is the ability to evaluate the robustness of the exposure classification.

In this thesis, Q-Q plots are used as an exploratory tool to investigate the appropriateness of a priori categorisations. When Q-Q analysis is carried out, it is done so in association with a priori ideas of categorisation, and often turns out to be a small adjustment in cutpoint that is appropriate for the population under investigation. Furthermore, these small changes in cutpoint tend to have little effect on the relationship of the independent variable in relation to the outcome. Where the Q-Q analysis shows the a priori categories
are inappropriate, the Q-Q categories are used (as using inappropriate *a priori* categorisation would lead to misleading results). An example of this has been shown previously in this chapter.

To investigate the effects of multiple comparisons, the final multivariate models will be shown along with the p-values associated with each of the variables in the model.

### 4.2 Definitions of Estimates of Risks

When using a binary outcome the measure of risk associated with the outcome is called “relative risk” (RR). In the case of a non-population study (such as a case-control study) the relative risk is approximated by the “odds ratio” (OR).

<table>
<thead>
<tr>
<th>Case</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Yes</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>c</td>
</tr>
<tr>
<td></td>
<td>N₁</td>
<td>N₀</td>
</tr>
</tbody>
</table>

In this situation:

$$RR = \frac{a \cdot M₀}{c \cdot M₁} = \frac{a \cdot (c + d)}{c \cdot (a + b)}$$

The relative risk is approximated in cross sectional studies by the odds ratio under the rare diseases assumption.

Confidence intervals for the odds ratio are calculated using the standard error (s.e.) which is estimated by the square root of the sum of the reciprocals of the cell sizes (i.e. the square root of $1/a + 1/b + 1/c + 1/d$).

Similarly using a logistic model (described below) and a single independent variable, a model is fitted where the odds ratio is estimated by the exponential of the parameter estimate for the variable i.e. OR=$e^{\beta_1}$, where $\beta_0$ is the intercept and $\beta_1$ the parameter estimate of the variable of interest. The confidence interval being the
exponential of the parameter estimate +/- the normal z-score times the standard error, the z-score being at the appropriate level for the confidence interval of interest. For example the 95% confidence interval would be \((e^{0.1 \pm 1.96 \times \text{se}}, e^{0.1 \pm 1.96 \times \text{se}})\).

4.3 Modelling Using a Binary or Continuous Outcome

4.3.1 Binary outcome

In the case of a binary outcome, modelling is best handled by the use of a logistic regression. The logistic model is simply a modification of the linear regression situation. We could use linear regression to calculate \(E[Y/x] \) (call \(\pi\)). However using linear regression would allow \(E[Y/x] \) to be negative. To overcome this we can build a linear model for the logistic function. The logistic function is defined as: \(g(\pi) = \ln \frac{\pi}{(1 - \pi)}\) 

In fitting a linear model to the logistic function we get:

\[
\ln \frac{\pi}{(1 - \pi)} = \beta X \quad ; \text{so,} \\
\]

\[
\frac{\pi}{(1 - \pi)} = e^{\beta X} \quad ; \text{so,} \\
\]

\[
\pi = \frac{e^{\beta X}}{(1 + e^{\beta X})} \\
\]

Hence logistic regression is based on the same principles as linear regression, with the exception that \(E[Y/x]\) is bounded by \([0,1]\), and the errors are binomially distributed. The method of maximum likelihood is used to determine the fit of the model. This is equivalent to the method of least squares in linear regression. The likelihood function is given by:

\[
\prod_i P_i^\pi(1 - P_i)^{1-\pi} \\
\]
When using logistic regression the log of this function is used, hence:

\[ \sum_i y_i \ln(\pi) + (1 - y_i)\ln(1 - \pi) \]

The main advantage of using a binary outcome is that when categorising independent variables, fitting these variables to the binary outcome produces a parameter estimate, which is the log odds ratio. The exponentiation of the log odds ratio (as previously described) produces the odds ratio for a specific group of individuals, assuming that coding of the categories is carried out appropriately. The odds ratio is seen as advantageous due to its ability to specify an increased or decreased risk for a group of individuals.

One can use continuous variables in modelling a binary outcome, this however leads to results for a variable that are often not easily interpreted.\(^\text{107}\)

The main disadvantages of using a binary outcome are: 1) loss of power if the variable is converted from a continuous variable to a binary one, 2) the results are in a ratio form rather than absolute values (although probabilities can be calculated from a cohort study), and 3) the requirement of appropriately categorised variables.

Logistic regressions were performed in SAS by the use of the LOGISTIC procedure\(^4\). The fitting of models was performed by modelling the outcome with the independent variables using dummy variables and corner constraints (the creation and description of which have been given previously). The LOGISTIC procedure fits a logistic model to the data as previously described and produces parameter estimates which correspond to the log odds ratios of the dummy variables (in comparison to the dummy variable representing the base category). An example of the use of the LOGISTIC procedure is given in Appendix B of this thesis.

4.3.2 Continuous Outcome

Continuous outcomes are modelled using linear and non-linear regression. The main advantage of using a continuous outcome is that this is often the natural form of the data collected. Thus the maximum possible information is being used as far as the outcome is concerned, and true effects of independent variables are not as likely to be hidden.
The use of a continuous outcome does not, however, prohibit the categorisation of independent variables in the case where they are themselves continuous but would be likely to lead to a loss of information with little benefit. This does lead to the situation, however, of an interpretation of the relationship between the independent variable and outcome. For example if a relationship that was quadratic was treated as linear it is likely to lead to misleading results.

When using a continuous variable the effects seen in the fitted model are of the change in the outcome variable, in this case birthweight, for every unit change in the continuous independent variable. In the case of dummy variables representing different levels of a categorical variable, the parameter estimate is an estimate of the difference between average birth weight in the specified group and that in the baseline group (adjusted for the effects of the other variables in the model).

The disadvantage in using a continuous outcome is interpretation of the size of the effects. For example, an effect of a 100g decrease in birthweight is likely to be significant, but the relativeness of a 100g decrease in weight is different in a 2000g baby to that of a 100g decrease in weight of a 3500g baby, being 5% and 2.9% respectively. Furthermore is the issue of a shift in mean birthweight having different consequences at the end of the distribution. A shift to the left in the birthweight distribution would change the percentage of infants less than 2500g from 2.7% to 3.9% amongst term infants in the NWH population. This is not such a problem in New Zealand but in other places where 2500g is towards the other end of the distribution this could have disastrous consequences.

Linear regressions were performed using the REG procedure in SAS. The models were fitted by placing the dummy variables in the model to predict birthweight. The REG procedure produces parameter estimates which are the changes in birthweight from the group represented by the dummy variable left out of the model. An example of the use of the REG procedure is given in Appendix C.

4.4 Methods of Data Analysis

4.4.1 Creation of Dummy Variables

Dummy variables are used in both the logistic and linear regression models in this thesis to describe the differences between groups of data. The range of an independent variable is covered by two or more dummy variables, with the number of dummy variables being equivalent to the number of categories being defined.
Each dummy variable covers a range of values of the categorical or continuous variable. Together the dummy variables (for an independent variable) cover its full range. Furthermore, the sum of the dummy variables relating to each independent variable, will have a sum of 1 for each observation. One of the ranges of values of the independent variable, (defined by one of the dummy variables), is usually designated as the base category. This is the category to which the other categories of the independent variable of interest are compared. The determination of the base category is entirely arbitrary but is usually that which is considered to be safest or normal (usually defined by the category containing the greatest number of observations), and this category by definition has an odds ratio of 1. The idea of dummy variables is best described by the use of an example.

Suppose we have a variable “ethnicity” that can take the values “Maori”, “Pacific Islander” and “Other”. Three dummy variables are set up, for simplicity call these Maori, PI and other. These three variables are assigned values according to the value of the variable ethnicity. If ethnicity has the value “Maori” for a given observation, then the dummy variable Maori will be equal to 1 and the other two dummy variables will be assigned the value 0 for that observation.

When the models are fitted, the dummy variable chosen as the base category is left out of the model, being the category with which the others will be compared. In the case of a logistic regression the parameter estimates produced are the log odds ratios, the exponential of which, is the odds ratio for that category in comparison to the category that was left out of the model (i.e. the base category). In the case of a regression with, in this case, birthweight as the outcome, the parameter estimates will be the difference between the average birthweight of the group, compared to the average birthweight in the base category.

The method of leaving a variable out of the model is known as using “corner constraints”. Another method of modelling entails putting all of the dummy variables for a variable in the model, known as “summation constraints”. In the case of the logistic regression, using summation constraints produces parameter estimates the exponential of which is in comparison to the mean of the sample. This can often be meaningless especially with such variables as ethnicity which do not have a mean. In the case of the continuous outcome the parameter estimate is the difference of that group from the population mean.

**4.4.2 Methods for Univariate Analyses**

The univariate analyses using the NZCDS data (see Chapter 5) and the NWH data (see Chapter 7) were carried out using the same methods. The binary outcome analysis was carried out using 2 way tables
and logistic regression as described in section 4.3.1. Calculating odds ratio from 2 by n tables and logistic regression produce identical results. These logistic models did not include any factors other than the variable of interest since, in effect, the definition of SGA (by using sex specific percentiles curves) controls for both sex and gestation. These odds ratios therefore show strict associations between the variable of interest and SGA.

Independent continuous variables are often divided into more than two categories. One of the reasons for this is the possibility of a dose-response effect. A dose-response effect can be tested at the univariate level by the use of a Chi-squared test for trend. Given the following table we can define several terms used in the calculation of a Chi-squared test for trend which has one degree of freedom. The x_i's in the exposure level are the midpoints of the exposure category.

<table>
<thead>
<tr>
<th>Exposure level</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a_0</td>
<td>b_0</td>
<td>m_0</td>
</tr>
<tr>
<td></td>
<td>a_1</td>
<td>b_1</td>
<td>m_1</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>a_t</td>
<td>b_t</td>
<td>m_t</td>
</tr>
<tr>
<td>Total</td>
<td>n_1</td>
<td>n_2</td>
<td>n</td>
</tr>
</tbody>
</table>

T_1 = \sum a_i x_i , \quad T_2 = \sum m_i x_i , \quad T_3 = \sum m_i x_i^2 \quad \chi^2 = \frac{n_1 n_2 (nT_1 - T_2^2)}{n^2(n-1)}

and \( \chi^2 = \frac{(n-1)T_1 - T_2^2}{n} \)

Furthermore, when the Chi-square for linear trend is subtracted from the overall Chi-square for difference between categories (with t degrees of freedom), one can test whether the overall difference is explained by the linear trend, using the critical value of a Chi-square test at a given level of significance with t-1 degrees of freedom.
The univariate analyses, using birthweight as a continuous outcome, are controlled for gestation but not infant sex. Gestation is controlled for since birthweight is known to increase with increasing gestation. Furthermore, gestation itself may be affected by the independent variable being considered.

Infant sex is not controlled for since it does not affect gestation. However female infants are known to be smaller than male infants. Unlike gestation there is no known reason why the independent variables being considered in relation to birthweight should have any effect on infant sex.

4.4.3 Methods for Multivariate Analyses

The multivariate analyses of the NZCDS (see Chapter 6) contain three multivariate models: 1) partial, 2) full and 3) reduced. The NWH data (see Chapter 8) only contains full and reduced models. The models using the binary outcome control for both gestation and sex, even though (as in the univariate case) they have essentially been controlled for by the definition of SGA.

SGA in this thesis is defined by sex specific birthweight percentiles, with the percentiles being produced from whole population data. The two datasets used in this thesis are not whole population data but samples, as previously described. The first (NZCDS) is a sample from the population over a time period that overlapped to some extent with the time from which the national data was used to produce the percentile charts. The second (NWH) data set was from a single hospital at a time point after that for which the percentile data was collected. It is therefore possible that the distribution of gestation and birthweight may differ in the samples in comparison to that in the percentiles. Furthermore it is expected that birthweight is increasing over time.

Whilst it is not essential to control for gestation and sex (since this is in effect done by the definition of SGA), it does not detract from the model apart from the loss of several degrees of freedom from the error term. It is also a way of checking that the samples do not differ significantly from the distribution of gestation and sex of the percentiles. This could happen by chance in sampling procedures or by a change over time. Hence gestation and sex have been controlled for in multivariate analyses as a precaution. Furthermore, this allows an estimate of the true difference in birthweights between the sexes and gestations to be determined after controlling for any potential confounders.

The two outcome perspectives (binary and continuous) are both considered in the partial, full and reduced model situations. These types of models are specified as follows:
i) Partial model: This model contains groupings of variables (for example socio-demographic). These models are aimed at looking at how variables of the same "type" are associated with the outcome after controlling for each other, and how these variables affect the other variables association with the outcome.

ii) Full model: This model combines all the groupings of variables.

iii) Reduced model: This model takes the full model described above for each of the outcome variables, and removes variables that are considered to have no significant direct or indirect effect on the model. The criteria of removing variables from the model was that they had a p value of greater than 0.05 and that removal of the variable did not have any discernible effect on the parameter estimates of the other variables. The order of removal of the variables from the model was determined by the size of the p value, the term with the highest p value being the next term removed from the model.

No formal testing of interaction was carried out. The investigation of interactions in the models was performed by removing each single variable from the full model and checking the parameter estimates of the other variables for changes in size.

Residuals from the linear regression models were checked for normality and are described respectively in the chapters containing the analysis.
Chapter 5: Univariate Results of the National Study

This chapter uses data from the control arm of the New Zealand Cot Death Study as described in Chapter 3. The data from the control subjects is considered here at the univariate level using birthweight to create outcome variables and to identify associations between these outcomes and variables associated with pregnancy. The univariate relationships of the independent variables to the outcome are considered in two ways:

a) The relationship of the independent variables to birthweight as a dichotomous variable, (being SGA), and having been defined as less than or equal to the 10th percentile for gestational age (see Chapter 2).

b) The relationship of the independent variables to birthweight when birthweight is considered as a continuous variable.

The independent variables were considered as 1) a priori categorisation, 2) categorisation as suggested by the method of Quantile-Quantile (Q-Q) plots (as described in chapter 4), and 3) where appropriate as a continuous variable.

5.1 Socio-demographic Variables

5.1.1 Socio-economic Status

Socio-economic status is derived from the occupations of the mother and father. The occupations of the mother and father were coded using the Elley-Irving revised socio-economic index for New Zealand. These codes fall into the following socio-economic groups; I (high) through VI (low) and VII (others). The family socio-economic status is determined by the higher of the mother's or father's socio-economic codings.

The obvious problem that arises from the use of this variable is that the occupation may not necessarily be a good indicator of the true family income or socio-economic status. Also the occupation codes very quickly become out of date: for example, the latest set of codes at time of coding in 1987 was published in 1976.
The standard *a priori* categories for socio-economic status are “high” (I,II), “middle” (III,IV), and “low” (V,VI) and “others” (VII). Using these categories and a binary outcome produces slightly unexpected results as shown in Table 5.1. In comparison to the “high” SES group, there is a small non-significant increase in risk for the “middle” class, but no increase in risk of having an SGA infant for the lowest SES group.

The Q-Q plot shows an entirely different picture (Fig 5.1). The most striking feature being the change in gradient moving from SES III to SES IV, i.e. the two “middle” class codings that are usually combined. The plot shows that SES II and III act at a similar level, and that SES V, VI and “others” also act at a similar level. The odds ratios (Table 5.1) again show little effect. In comparison to those in SES I those in SES IV are at a higher risk of having an SGA infant, though this is not significant, and the other groups show small non-significant decreases in risk. The use of the Q-Q plot has achieved the detection of the difference between the SES III and IV groups that usually form the joint “middle” SES status group. The effects of SES II/III and IV are actually of opposite directions, in comparison to the base category.

Using these categories with a continuous outcome for birthweight gives a slightly different picture (Table 5.1). In the *a priori* case both the “middle” and “low” socio-economic categories have a significantly decreased birthweight compared to the “high” socio-economic group. Both these differences are of a similar size. This differs from the binary outcome where there was almost no effect of low socio-economic status.

Using the Q-Q plot categories, the decrease in weight for SES categories II and III are not significantly different from those in SES I. The other two categories (IV and V,VI,others) are however significantly different. The point estimate of those in SES IV being larger than that for the lowest SES grouping.

Socio-economic status is not suitable for modelling as a continuous variable.

Very little is to be seen in the way of a significant relationship of socio-economic status at the univariate level using the binary response. This may in part be due to the classification technique, both due to the method and to the age of the most up to date SES codes. Even though the Q-Q plot shed some light on possible re-grouping of socio-economic classifications, these new groupings had little effect in the model when SGA was considered as the outcome.

The use of a continuous outcome shows more of an effect, and is also more consistent with what may be expected. Again, this is seemingly better with the use of the Q-Q categories. In the United Kingdom, socio-economic codings fall into two broad categories ‘manual’ and ‘non-manual’. The results using a continuous
outcome suggest two broad groupings may be appropriate for use as socio-economic status. The Q-Q categories seem to be the more appropriate to use in the multivariate analysis given the contrary results between these and the *a priori* categorisation.

### 5.1.2 Maternal Education (i.e. age mother left school)

The age the mother left school is an indicator of the mother’s educational level. It is defined here from the question "At what age did you leave school?". This is measured as an ordinal variable, and, as such, is of a continuous nature (although the variable has a limited range).

From an *a priori* view, there are three broad categories of this variable: no qualifications, some qualifications, and completed school. As such the *a priori* categories are; less than 16 years of age, 16 years of age, and greater than or equal to 17 years of age, when left school. Whilst age is probably not the best way of categorising educational level, it is the best indicator of maternal education status available in this dataset. A more appropriate measure may have been to categorise mothers on the actual level of educational achievement (e.g. school qualifications, academic and trade related tertiary qualifications). However, as SIDS cases in the original case-control study were likely to have few qualifications, age when left school was seen to be more appropriate at the time of the study.

The Q-Q plot for the age mother left school (Fig 5.2), shows points for completed years of age, such that those between the points marked 16 and 17 were 17 years of age when they left school. One can see that almost all mothers left school after reaching 14 completed years of age and before reaching 19 completed years of age. However, there are small numbers of mothers who left school very early or late in age. The Q-Q plot suggests an increased risk for those who were less than 17 and this was further increased if they were less than 15, in comparison to those who left after reaching 17. It may be appropriate to combine the groups of less than 15 and less than 17 due to the small number of observations in the less than 15 group. The plot also suggests an increased risk for those who were greater than 17. These may be mothers who stayed at school later due to repeated years, however there is no way of checking this. It may be sensible to combine these with the 17 year old category due to small numbers. So the categories suggested by the Q-Q analysis are; less than 15, 15-16, the comparison category of 17, and those 18 or older.

Using SGA as the outcome with the *a priori* and Q-Q categorisations, produces the results shown in Table 5.2. The *a priori* categorisation shows what we would expect; an increased risk for those who left school at
16 and a larger risk for those who left before the age of 16, in comparison to those that left after 16 years of age, both being significant at the 5% level. The odds ratios from the categorisation due to the Q-Q plots show a more detailed pattern. The younger the mother was when she left school, the greater the risk, as in the a priori case, though this categorisation by definition produces larger odds ratios. There also seems to be a tendency (though non-significant) towards an increased risk if the mother was older than 17 years old when she left school, suggesting that this group may well include some mothers who had to repeat years at school. However, this group could also contain some mothers that are older than 17 due to when their birthdays fell within the school year, or have left and then returned, and hence it is likely that it would be best to combine these two groups to make a comparison category of 17 or older.

Considering birthweight as a continuous variable and fitting a linear regression model controlling for gestation with these same categories shows a similar pattern to the binary outcome. The results are shown in Table 5.2. Using the a priori categories, there is a significant decrease in weight seen for those who left before 16 years of age, and a smaller not quite significant decrease in birthweight for those who left at 16. Using the Q-Q selected categories again shows a more detailed pattern, those 18 or older showed a small non-significant decrease in birthweight. Compared to those who left at 17, those who left at 15-16 showed a moderate decrease, and those less than 15 showing a much larger decrease in birthweight, both these results are significant at the 5% level. These decreases in birthweight fit well with the odds ratios found using SGA as the outcome.

Looking at the univariate analysis for the Q-Q categorisation, the much larger decrease in birthweight and the larger magnitude odds ratio shown for those less than 15 (Table 5.2) suggests avoiding combining this age group with the less than 17 category. However, those that are in the 18 or older group will be combined with the 17 year old age group. The results are those expected as shown in Table 5.2.

The age the mother left school is itself a continuous variable and hence could possibly be fitted in its raw form. Doing this however would be inappropriate as the pattern shown by the odds ratio suggests that the relationship is not a linear one. Also the range of this variable is limited, and the values recorded are discrete. Fitting a higher order term such as a squared term would also be inappropriate as the relationship is obviously not symmetrical.

Summarising for this variable, it seems that the a priori choices are inappropriate as they do not fully describe the relationship between the outcome and the age the mother left school. The categories chosen using the Q-Q plot approach do show the full pattern and give similar results with both the binary outcome and
continuous outcome approach. Using age mother left school as a continuous variable poses some problems due to its limited range and non-linear relationship.

5.1.3 Marital Status

Marital status is often an indicator of maternal support, in that it describes whether the mother is in a relationship that is likely to be providing some support. Marital status is also related to such variables as SES and young maternal age. The a priori categories for this variable are usually married/unmarried, however this may not be the most appropriate choice. Given the consideration that this variable is being used as an indicator of maternal support and other socio-demographic factors, it may be more appropriate to categorise this variable as single versus others, since nowadays people often live in unmarried relationships; or could be divided further into three categories; single, defacto and married. The mothers who are difficult to categorise in this situation are those who are single at the time of questioning, due to divorce, separation, or being widowed, though small in number (4 SGA cases, 37 SGA controls). These mothers have been placed in the single category since this is their current status, though we are unable to determine when this event occurred, from the available information.

Considering SGA as the outcome (Table 5.3), there is a significant increase in risk of having an SGA infant if the mother is not married compared to those who are married. However if this unmarried group is broken down further by separating out those in a defacto relationship, the SGA risk for those in the group who are in defacto relationships is no different to those who are married. Those who are single are at an increased risk.

Looking at birthweight as a continuous outcome and considering these same categorisations of marital status, we see a similar pattern. There is a significant decrease in weight of the infants of those mothers who are unmarried in comparison to those who are married. This decrease in weight is almost double if the categorisation of single versus married is used. There is however, no difference in decrease in birthweight when the defacto mothers are compared to the married mothers. The results showing consistency between the odds ratios and the decrease in birthweight.

Both the binary outcome and continuous outcome show very similar relationships with marital status at the univariate level for both responses. It seems the more appropriate categorisation with this data is; single vs others as opposed to married vs others, and that those in defacto relationships can be categorised with those being married.
Maternal social support is conceptualised as an intervening variable and has been found to ameliorate the effects of environmental stress on specific complications of pregnancy and delivery. The Maternal Social Support Index (MSSI) is an index developed to quantify the aspects of mothers’ social support networks that may be related to their ability to provide their children with safe, warm, and stimulating environments. The MSSI has been validated and hence the suggested scoring system was used. The possible range for the MSSI score from a low of 0 to a high of 19 and is an integer score.

The a priori categorisation was to define maternal social support as high or low, using a cutoff point of less than or equal to 10. This cutoff had been determined in a previous analysis, using this dataset (unpublished data), as the cutoff that maximises the odds ratio when splitting MSSI into two categories. This cutoff showed an increased odds ratio (Table 5.4) for those mothers who had "low" maternal social support which included approximately 35.0% of the mothers of SGA infants in comparison to 24.9% of the controls.

The Q-Q plot (Fig 5.3) suggests something a little different actually exists than a straight high/low social support. The plot shows a relatively constant risk for those mothers whose MSSI score is less than or equal to 10, and then a steady decrease in risk for those with MSSI scores between 11 and 13. The additional feature that the Q-Q plot shows is the increasing risk for those mothers who have scores greater than 13. The odds ratio though is not large and does not reach significance, suggesting the high/low cutoff of the a priori categories may be more suitable.

Consistency is again apparent when we consider the continuous outcome (Table 5.4). Using the high/low split, those with low maternal social support (i.e. MSSI less than or equal to 10) gave birth to infants with significantly decreased birthweights. Using the categories as suggested by use of the Q-Q plots, there is a significant decrease in birthweight for those mothers with an MSSI less than or equal to 10, but only a slight decrease in birthweight for those mothers whose MSSI was greater than 13. This is consistent with the odds ratio produced when using the binary outcome.

The MSSI is a continuous variable and as such it may be appropriate to describe a certain decrease in weight for every point decrease in the MSSI. The Q-Q plot categories however, suggest that the relationship between birthweight and MSSI is not linear. Also the increased risk of low and high MSSI scores is not of the same magnitude, making it difficult to model the continuous variable as a quadratic term.
The relationship between maternal social support and birthweight is somewhat unusual. There seems little doubt that lack of maternal social support is associated with an increased risk of a SGA infant or that when using a continuous outcome there is a decrease in birthweight with low scores. Both the binary and continuous outcomes give similar results. The Q-Q plot suggested a possibility of increased risk if the MSSI was too high (though this was not significant), and again the binary and continuous results were consistent. Similarly these methods show that MSSI is not appropriate to be used as a continuous variable.

The preferred categorisation therefore seems to be the *a priori* categorisation which maximises the odds ratio of the ‘at risk’ group. Even though significant, the increased risk or decrease in birthweight, depending on the outcome used, is not of a large magnitude.

### 5.2 Maternal Lifestyle Factors

#### 5.2.1 Maternal Smoking

Maternal smoking is an extremely important factor in relation to SGA. However it is also confounded by a number of variables, especially those of a socio-economic nature. The *a priori* categories are; non-smokers, smoke 1-9 per day, 10-19 per day, and 20 plus per day.

The results show that the non-smokers are at the lowest risk of having an SGA infant. Smokers, depending on the number of cigarettes smoked per day, have an increased risk with an odds ratio between 1.5 and 3.25 of an SGA infant (Table 5.5). The interesting point to note from the *a priori* categories is the slightly but not significantly lower risk of those smoking 10-19 per day as opposed to those smoking 1-9 per day relative to the non-smokers. A test for linear trend gave a highly significant $\chi^2=27.368$ (p<0.0001), the overall $\chi^2=30.220$, the difference between these is 2.852 with 2 degrees of freedom, which shows that the linear trend accounts for the majority of the difference observed. Using birthweight as a continuous outcome shows an effect such that birthweight decreases as the number of cigarettes per day increases.

The Q-Q plot (Fig 5.4) suggests an additional split of the smoking category 1-9, into 1-4 and 5-9. The odds ratio (Table 5.5) shows that the group that only smoke 1-4 cigarettes per day are still at an increased risk, though this is not significant at the univariate level, possibly due to the small number of subjects. The other thing this additional split does is to enhance the difference in the odds ratios of the 5-9 and the 10-19 per day groups. Again a test for linear trend finds a highly significant result $\chi^2=29.237$ (p<0.0001). The overall
\( \chi^2 = 33.140 \), so the difference again shows that the linear trend accounts for most of the observed difference. Using these categories with birthweight as a continuous variable also has the same unusual aspect, with the decrease in birthweight slightly larger for the 5-9 group than for the 10-19 group.

The number of cigarettes per day is difficult to use as a continuous variable itself due to the fact that when people are asked how many cigarettes they smoke per day, the answer tends to be in multiples of five. For instance, 64.4\% of both cases and controls that smoked answered in this manner. For this reason, no attempt will be made to use the number of cigarettes smoked per day as a continuous variable.

The increased risk of an SGA infant from smoking ranges from approximately 1.5 for the lightest smokers to over three times the risk for heavier smokers. Similarly, the decrease in birthweight is 38g for the lightest smokers, and 249g for the heavy smokers (which can be 10\% of an infant’s birthweight). This may account for much of the variability in birthweight, however the \textit{a priori} and Q-Q categories accounted for only 3.74\% and 4.26\% of the variability respectively.

There is little doubt of the importance of maternal smoking in relationship to SGA infants. Though the relationship at the univariate level is not quite as expected, there are a number of variables that confound with maternal smoking and it is possible that there may well be a stronger dose-response relationship, once these confounders have been controlled for. There is little doubt though of the extremely high risk of having an SGA infant amongst heavy smokers.

### 5.2.2 Marijuana Usage

Marijuana smoking is reported by 5.6\% of the control mothers and 13.5\% of SGA mothers. The measurement here is simply whether it was used during pregnancy or not.

The odds ratio (Table 5.6) shows the effect of smoking marijuana. Those that smoked marijuana during pregnancy are more than two and a half times more likely to have an SGA baby. This effect is also emphasised and consistent when birthweight is used as a continuous variable. Those who smoked marijuana during pregnancy have babies on average nearly 200 grams lighter than other mothers.

It is important to keep in mind that marijuana smoking is likely to be confounded, especially by cigarette smoking, since almost all smokers of marijuana in this dataset also smoked cigarettes.
5.2.3 Alcohol Consumption

Maternal alcohol consumption is difficult to measure both because of the many different types of alcohol and the problems associated with collecting data on the amount of alcohol consumed.

The problems relating to the type of alcohol consumed have been overcome here by using the number of glasses of alcohol drunk per week. This measure can be used since the amount of alcohol in a glass of beer, glass of wine and nip of spirits are approximately equal. There is little chance of improving the collection of amount actually drunk as opposed to that reported since this data was collected retrospectively.

Because it is difficult even to guess how much alcohol the "average" person drinks during a week, it is difficult to decide on *a priori* categories, apart from the category of non-drinker. Therefore, categories were decided upon by "eye-balling" the data and producing a Q-Q plot of the number of drinks per week. This was done for both the first trimester (Fig 5.5a) and the last trimester of pregnancy (Fig 5.5b).

The data suggests dividing alcohol consumption into the following categories; non-drinking, 1-4 drinks as "moderate" drinking, and 5 or more drinks per week as "heavy" drinking. This was consistent using data from both the first trimester of pregnancy and the last trimester of pregnancy. It is interesting to note that almost all those in the moderate group, drink one or two drinks a week, and hardly any drink 3-4. The categories are therefore relatively easy to define.

The results of drinking alcohol in both the first and last trimester are very similar (Table 5.7). The odds ratios for the moderate drinkers are both very close to unity suggesting no difference between the moderate drinkers and the non-drinkers. The odds ratios for the heavy drinkers however are significantly different from unity and show that heavy drinkers are more likely to have an SGA baby. A test for linear trend of alcohol consumption in the first trimester gives a $\chi^2=6.644$ (p=0.001) in comparison to an overall $\chi^2=13.18$, the difference of 6.536 with 2 degrees of freedom (p<0.05) shows that the pattern of linear trend does not fully describe the pattern of alcohol consumption. Neither an overall difference between categories ($\chi^2=4.700$ (p=0.0952) or a linear test for trend ($\chi^2=2.258$ (p=0.1330), for alcohol use in the last trimester were significant.

Using birthweight as a continuous variable gives results that are similar for both first and last trimesters of pregnancy and are consistent with the results given by the odds ratios. There is little difference in birthweight
of babies of non-drinkers and those of the moderate drinkers. However, babies of heavy drinkers have significantly lighter birthweights.

It is also of interest to see that the amount of drinking from the first trimester to the last trimester has also decreased. The number of drinkers in the moderate category is about the same, however the number of heavy drinkers has decreased and the number of non-drinkers has increased. This decrease in the amount drunk is mainly a general downward effect, such that moderate drinkers become non-drinkers and heavy drinkers become moderate drinkers between the first and last trimesters of pregnancy. Naturally there are a small number of exceptions to this general trend, as in the case of some non-drinkers becoming drinkers.

Binge drinking is difficult to determine by using this method of measuring alcohol since only the number of drinks per week is being considered and not how often the mother was drinking to consume this amount of alcohol.

Therefore the effects and numbers of drinkers in the first trimester are greater than the last trimester, so the first trimester will be used in further analysis. The first trimester is also the time of development of many important structures in the fetus, when alcohol is most likely to have a detrimental effect.

Summarising it seems that there is no increase in risk of a SGA infant with moderate drinking in pregnancy, although there is an increased risk for heavy drinkers. As with other variables, maternal alcohol consumption is likely to be confounded by other variables, especially cigarette smoking, marijuana smoking, and other socio-economic type variables.

5.2.4 Caffeine Intake

Like maternal alcohol, the amount of caffeine intake by the mother during pregnancy is also difficult to measure since it is reported retrospectively and the amounts of caffeine are different in different drinks. The amount of caffeine in different drinks however, is not as easily solved as with the alcohol consumption since one cannot just count the number of drinks. For this reason it has been necessary to calculate the amount of caffeine consumed from the different drinks of coffee, tea and cola as reported by the mothers.

Looking at whether or not these three drinks were consumed by the mother during pregnancy (Tables 5.8a, 5.8b) revealed that coffee and cola showed a slight non-significant increased risk, and tea showed no difference at all. These results were consistent for both the first and last trimester though a little higher in the
first trimester. Using birthweight continuously showed slightly different results, i.e. small non-significant changes in birthweight amongst infants of both tea and cola drinkers. This was true for both the first trimester and last trimester as shown in the tables (Tables 5.8a, 5.8b). The coffee drinkers however showed an almost significant decrease in weight if consumption was in the first trimester, and a significant decrease in weight if consumption was in the last trimester. It is also noticeable that mothers do not seem to change their caffeine intake during pregnancy.

The amount of caffeine consumed was therefore calculated as the daily total. The data was split into 100 mg groups to check for any dose-response or threshold effect. Consumption was split in a similar manner to alcohol with the use of a Q-Q plot, into; “non-consumers”, up to 600 mg of caffeine being "moderate" (which is the equivalent of either 6.5 cups of coffee or 8.5 cups of tea per day), and above 600 mg as being "heavy".

Like alcohol consumption, the risks associated with caffeine consumption in both the first (Fig 5.6a) and last trimesters (Fig 5.6b) of pregnancy are similar. Those with a moderate intake of caffeine had slightly but not significantly increased risks (Table 5.8c) of an SGA infant. Those with a large intake of caffeine however are almost twice as likely to have an SGA infant. This does not quite reach significance in the first trimester, but reaches significance in the last trimester. Tests for linear trend were not carried out as overall Chi-squares for caffeine use in the first ($\chi^2=3.00$ (p=0.2234)) and last ($\chi^2=5.60$ (p=0.0608)) were not significant at the 5% level.

Using birthweight as a continuous outcome, we find results along similar lines, however the increased amount of information from birthweight makes the differences more easily detected. It can be seen that those moderate consumers of caffeine in the first and last trimester have a decrease in birthweight, with the last trimester not quite significant at the 5% level. This decrease in birthweight seems to be larger than that suggested by the odds ratios. The heavy consumers of caffeine both in the first and last trimester have significantly smaller infants.

Considering whether any caffeine was consumed (Table 5.8c) shows that the risk is not-significant when SGA is considered as a binary outcome. However, using birthweight as a continuous variable shows a significant decrease in birthweight of babies born to mothers who have consumed caffeine during pregnancy. The results in the table however, suggest that the amount of caffeine consumed has some importance, hence caffeine consumption as a binary variable does not provide sufficiently detailed information.
In summary, it appears that at a univariate level, mothers who consume large amounts of caffeine during pregnancy (>600 mg daily), are at a greater risk of having an SGA infant. This is consistent when birthweight is used as a continuous outcome. Looking at the individual sources of caffeine suggests that this risk may be due mainly to the consumption of coffee. This may be an effect of the caffeine in conjunction with another substance in the coffee or may simply be a chance effect.

The size of the effects in both first and last trimesters are very similar so first trimester use will be used in further analyses as in the case of alcohol consumption.

5.3 Genetic Factors

Adult size may differ between ethnic groups due to genetic differences, as noted in Chapter 2, which in effect could influence the birthweight of the baby. As mentioned in the literature review, none of the factors considered under this heading have conclusive genetic properties, and any effect due to ethnicity may be due to cultural differences as opposed to genetic ones.

5.3.1 Ethnic Group

Ethnic group was considered for the possibility of a genetic and cultural ethnic effect on the size of the fetus. New Zealand has three ethnic groups that make up the majority of the population, these being; Maori, Pacific Islanders, and Europeans (though the number of Asians is starting to grow). Hence the a priori categories are Maori, Pacific Islanders, and others. Q-Q plot analysis is unsuitable since ethnic group is a categorical variable.

Consideration of this variable using a binary outcome shows that there is a slight but significant increase in risk of an SGA infant for those who are of Maori ethnic origin, but little difference for those of Pacific Island origin in comparison to the "others" (Table 5.9). The difference between the Maori and Pacific Island groups has already been discussed in relation to percentile curves (see Chapter 2).

Considering birthweight as a continuous variable and controlling for gestation shows a similar trend, i.e. Maori infants being significantly smaller than Europeans. Pacific Islander infants are larger than Europeans, and the point estimate is of approximately the same size as that between Maori and European, though in the
opposite direction. This difference in birthweight is also significant, in contrast to the effect seen using the binary response.

At the univariate level there is a relationship between SGA and ethnic origin. This relationship is difficult to interpret however at this time due to the confounding that is likely with other variables such as socio-economic status and maternal smoking.

5.3.2 Maternal Height

Maternal height was measured in cm (or in feet and inches then converted into centimetres). These measurements were self reported so it is likely that there is some inaccuracy in the measurements.

A priori categories for height are not easy to determine, so an attempt was made to categorise them into three groups; "short" (<=160cm), "average" (161-170cm) and "tall" (>=171cm). Using these categories (Table 5.10), mothers classified as being short in stature were at an increased risk of giving birth to an SGA infant. The odds ratios also showed that mothers in the "tall" group were less likely to give birth to an SGA infant, though this wasn't significant. An overall test for differences between the groups was found to be significant ($\chi^2=17.43$, p=0.0002) as was a test for linear trend ($\chi^2=16.512$, p<0.0001), the difference between these of 0.918 with 2 degrees of freedom showing that the linear trend accounts for the majority of the pattern.

Considering birthweight as a continuous outcome gave similar results for these a priori groups. Babies of the "short" mothers being 119 grams smaller on average than babies of mothers of "normal" height. Babies of the "tall" mothers were larger by 89 grams, than those babies of mothers of "normal" height. Both these results were significant (Table 5.10).

The range of heights was from 132 cm to 195 cm, though the number of observations were small towards the extremes. Over 97% of the observations were between 150 and 180 cm. Also some blocking at certain measurements was noticeable due to the conversion of feet and inches to centimetres.

After consideration of the Q-Q plot (Fig 5.7), it seems the ideas used to determine the a priori categories were quite reasonable (there seemingly being a distinct group of "short" mothers, and of "tall" mothers).
cut points differed slightly from those guessed for *a priori* choices, however this variable seems to emphasise the usefulness of the combination of *a priori* ideas and the suggestions of the Q-Q plot.

Using the cut points suggested by the Q-Q plot, in comparison to the "average" mothers, the "short" mothers had a significantly increased risk of an SGA baby, in contrast to the "tall" mothers where the odds ratio was in the protective direction, but of a similar magnitude. As in the *a priori* situation, the overall ($\chi^2=24.85$, p<0.0001) and test for linear trend ($\chi^2=23.053$, p<0.0001) were significant, the linear trend accounted for the majority of the pattern. Using birthweight as a continuous outcome gave results that are consistent with these odds ratios so that "short" mothers have smaller babies and "tall" mothers have larger babies. Again the results are of a similar magnitude and are both significant.

The results of these categorisations appear to show a trend. That being the shorter the mother, the more likely she is to have a smaller infant. This leads to the question as to whether we should therefore use maternal height in its natural form (like that of birthweight) as a continuous variable. Both the odds ratios from the binary outcome and the decreases in birthweight from the continuous outcome, suggest a linear term may be appropriate to use for maternal height.

Using maternal height as a continuous outcome shows that for every cm of height, there is an increase in birthweight of the infant of 10.82 grams (for example a mother of 173cm of height would give birth to a baby 108.2 grams heavier than a mother of 163cm). This term appears to be consistent with the results previously discussed.

Maternal height appears to be suitable for use in both the categorical form (using the Q-Q categories) and in its continuous form. The continuous form will of course provide more information than the categorical form, though this may prove more difficult to interpret, especially using the binary outcome.

### 5.3.3 Maternal Pre-pregnancy Weight

There is naturally a correlation between maternal height and maternal weight. Hence one may expect there to be similar trends with maternal weight in relation to birthweight as those shown with maternal height. These two measurements will not be perfectly correlated as people vary quite widely in shape and size (e.g. some people are "short and fat" some "tall and skinny"). So it is quite possible that both measurements may be
needed in the model. The correlation between maternal height and weight was 0.30 for all mothers in this data for which both measurements were recorded.

Measurements of maternal weight are self reported and may therefore contain a degree of inaccuracy. Also some weights have been converted from stones and pounds to kilograms possibly adding to error.

Similar ideas have been used to choose a priori categories as with maternal height, using the concept of three categories; "less than average weight" (<=50 kg) (as used in studies discussed in the literature review), "normal weight" (51-70 kg), and "greater than average weight" (>70 kg).

These a priori categories give a result similar to those with maternal height (Table 5.11). The mothers in the "less than average weight" group are at greater risk of having an SGA infant than the "normal" mothers, and "greater than average weight" mothers have a slight (though non-significant) decrease in risk of having an SGA infant. A test for overall difference between the groups was significantly different ($\chi^2=21.23$, $p<0.0001$), similarly a test for linear trend was significant ($\chi^2=12.424$, $p=0.0004$). Unlike maternal height however the difference between these $\chi^2=8.806$ shows that a linear trend does not fully account for the pattern with this variable.

Using birthweight as a continuous outcome, the results are consistent, the "less than average weight" mothers, gave birth to babies that were on average 290 grams smaller than the "normal" mothers. The result for the "greater than average weight" mothers is in the direction suggested by the odds ratio, in that these mothers give birth to heavier babies than the normal mothers. Unlike the odds ratio though, this difference is significant. It is also interesting to note that the increase in weight of these babies is not as large as the decrease in birthweight for the babies of "less than average weight" mothers.

Again the Q-Q plot (Fig 5.8) suggests that the a priori grouping ideas were of the right nature. The Q-Q plot does however suggest more than the three groups. It suggests additional categories for "slightly less than average weight" and "slightly more than average weight" (though the "slightly more than over average weight" group is low on observations). The odds ratios suggest that the "less than average weight" mothers are four times as likely to have an SGA baby, and "slightly underweight" mothers twice as likely to have an SGA baby than "normal" weight mothers. The two "greater than average weight" groupings are a little confusing; one suggesting a slight decrease in risk, while the other a slight increase, though neither is significant and both are close to unity. Like the a priori situation the overall ($\chi^2=30.99$, $p<0.0001$) and the
test for linear trend ($\chi^2=17.356, p<0.0001$) were significant, and the difference between them $\chi^2=13.634$, shows that the linear component does not describe the full pattern of this variable.

The use of birthweight as a continuous variable shows consistent results to those of the odds ratios for the "less than average weight" groups, but suggests an increase in birthweight for babies of mothers in the "greater than average weight" groups. The increase in weight for the "greater than average" groups are at a similar level and could be combined. These point estimates are of similar magnitude to the decrease in the "slightly underweight" group.

The decreases in birthweight suggest that it may be appropriate to use maternal weight as a continuous variable. Doing this gives a model that shows an increase in birthweight of 8.16 grams for every kilogram of mother's weight (for example, a mother of 70kg would give birth to a baby 81.6 grams heavier than that of a 60kg mother). The changes in birthweight and the test for linear trend using the binary outcome however suggest that the relationship is not entirely linear. For these reasons maternal weight will not be used as a continuous variable.

### 5.3.4 Maternal Body Mass Index (BMI)

Maternal body mass index (BMI) may be an appropriate measure to use instead of maternal height and weight, since individually these two variables make no consideration of "size and shape". Using maternal body mass index however, allows us to determine appropriateness of weight for height. The maternal body mass index is calculated by:

$$\text{BMI} = \frac{\text{maternal height (m)}}{\text{maternal weight (kg)}^2}$$

Only Q-Q plot categories will be considered as a priori categories for women before pregnancy are not known.

The Q-Q plot (Fig 5.9) suggested that there were three categories for the variable BMI; "light for height", "normal", and "heavy for height". The binary response (Table 5.12), shows that those who are in the "light for height" group are more than twice as likely to have an SGA infant as the "normal" mothers. The odds ratio for the "heavy for height" mothers is in the protective direction and not significant. The difference between the overall difference between the groups ($X^2=12.89, p=0.0016$) and the test for linear trend.
(X²=10.312, p=0.0013) is 2.578 with 2 d.f. implying most of the difference is accounted for with the linear trend.

Using birthweight as a continuous response confirms the pattern of the odds ratios with the babies of the "light for height" group being on average more than 150 grams lighter than those of the "normal" mothers. The use of the extra information from birthweight allows us to see that infants of the "heavy for height" mothers are in fact significantly larger than those of the "normal" mothers, though the difference is only about half the magnitude of that seen in the "light for height" mothers.

Maternal BMI is in fact continuous. Use of BMI in this manner shows a significant increase in birthweight of 15.18g per unit of maternal body mass. Hence this suggests that like maternal height and weight, BMI could be used as a continuous variable. However the differences seen in the "light for height" and "heavy for height" women were not of the same magnitude, suggesting that the effect may not be linear as implied in the categorical situation.

This variable does seem to be more appropriate to use than both maternal weight and height since it takes into account the importance of weight and height together.

5.4 Obstetric Factors

5.4.1 Maternal Age

Maternal age is a continuous variable ranging from mothers giving birth to babies from mid-teen years to the late thirties and early forties. For this reason there is likely to be a large amount of confounding between maternal age and parity. The \textit{a priori} categories for maternal age are reasonably broad, with categories for young and for older mothers, with the other mothers split to create two categories between 20 and 30.

The odds ratios for the \textit{a priori} categories (Table 5.13) show no pattern and none of the groups have any significant increase in risk. A test for overall differences between the groups (X²=1.83, p=0.6078) was insignificant. Using birthweight as a continuous variable however shows more pattern. This suggests decreasing birthweight as maternal age decreases. All these differences in birthweight are statistically significant at the 5% level.
The Q-Q plot (Fig 5.10) for maternal age shows why there was little effect in the odds ratios when we used the \textit{a priori} categories. The plot shows no pattern, but in general, identifies an equal risk right across the age range. Due to this trend, no attempt has been made to create categories from the Q-Q plots as there are no changes in the gradient of the plot.

Using the mother’s age as a continuous variable, itself in the form of a linear term, conforms to a similar pattern to the decreases in birthweight shown with the \textit{a priori} categories; an 8.47 gram increase in weight for every year of maternal age (Table 5.13).

As far as categorisation is concerned, the best way to handle this variable is to use common sense \textit{a priori} categories as there is no other sensible way to choose appropriate categories. There seems to be consistency with the linear term in these categories when birthweight is used as a continuous variable, but not when a binary outcome is used. Hence, either \textit{a priori} categories or maternal age continuously, will be used in further analyses. Maternal age is however confounded by a number of variables such as parity and maternal size.

\textbf{5.4.2 Urinary Tract Infection}

Urinary tract infection (UTI) is measured as a simple yes/no variable for whether the mother had a urinary tract infection during pregnancy. Although it was obtained from both the parental interview and the obstetric records, the obstetric information was used since it was more complete and is considered to be a more accurate definition of UTI. Therefore the only real consideration here is whether there is consistency between the binary and continuous response.

As is shown in Table 5.14, considering the outcome as SGA, there is a slight non-significant risk of a SGA infant if the mother had a UTI. Considering the outcome as a continuous variable, there is a decrease in birthweight which is also non-significant at the 5% level.

Using the binary and continuous outcomes produces consistent results that suggest a possible effect from UTI, though it is non-significant at the univariate level. This is likely to be due to the small numbers of women that have a UTI during pregnancy.
5.4.3 Antenatal Care

Antenatal care is measured here by the number of completed months the mother was pregnant when antenatal care was first given. This is also likely to be a reasonable measure of how much antenatal care was received during the pregnancy as those who attend relatively early in their pregnancy are likely to continue to go on for further checks. The actual number of visits attended would be difficult to measure and open to much larger error than the measurement of when first attended.

A priori categories are along the simple lines of “early” antenatal care and “late” care. These a priori categories show much of what we would expect from the variable split like this, that is; there is a significantly increased risk of an SGA infant if attendance at antenatal care is not until after the first three months of pregnancy (Table 5.15).

The method of Q-Q plots (Fig 5.11) show more of a pattern than the simple a priori categories. The odds ratios from the binary outcome increase for those who leave antenatal care till later than within three months of their pregnancy. There is however, an unexpected risk for those who first sought antenatal care before a month of completed pregnancy. This group of women, even though very small (3 cases, 9 controls), are unusual in that it is unlikely that they actually knew they were pregnant at this time. The question raised is why they were attending antenatal care. Possible reasons are that it was being done in the expectation of becoming pregnant, or the mother was under strict obstetric management.

With a continuous response, the a priori categories show a significant decrease in birthweight for those who first had antenatal care after the first trimester, as suggested by the odds ratios. However, the model using the Q-Q plot categories produces results that are different from those suggested by the results produced using the binary outcome. Those who attended at 0 completed months of pregnancy actually have heavier babies, though this does not reach significance. This discrepancy is likely to have occurred due to the small number of mothers in this group. Those that first attended at 2-3 months are only 12 grams heavier than those who attended at one month, which is non-significant. This suggests that those who attended before 1 month should be combined into the 1 month category, as should those who first attended at 2-3 months, hence a return to the a priori categories.

The best categorisation here depends on the outcome that is to be used. In the case of the binary outcome, the Q-Q plot categories seem to show a dose-response type effect with regard to the likely amount of antenatal care received. The continuous outcome however, favours the a priori categories, as this model
shows no differences between attendance at one month of pregnancy and either 0 or 2-3 months of pregnancy after adjusting for gestation.

5.4.4 Multiple Birth

Multiple birth is a yes/no variable, and no consideration of birth order has been made due to the small numbers of multiple births in the dataset. It is known that infants from multiple births are smaller so it may be considered that these infants be left out of the analysis. However the percentile curves that were derived in Chapter 2 contained multiple births so multiple births have been retained in the analysis.

As can be seen from the Table 5.16, there is a much increased risk of being an SGA infant if the infant is part of a multiple birth; the odds ratio being 4.10. Consistently, infants of multiple births are 479g lighter on average than those who are singletons when a continuous outcome is used.

5.4.5 Parity

Parity is an important factor in relation to an infant's size. Primiparous mothers are generally expected to have smaller infants. The data for the number of pregnancies was able to be considered from both parental interview and obstetric records. There was little difference in the two sources of information, the two sources having a sensitivity of 97.9% and a specificity of 98.0%, using categories for nulliparous and non-nulliparous mothers. Due to the good agreement between the sources of data, information obtained from the obstetric records was used since it was available for a greater number of women.

The a priori categories for parity are; primiparous, each of the next 2 pregnancies by themselves, and mothers with more than 2 previous pregnancies. The odds ratios (Table 5.17) are much like one would expect them to be in light of the above. The primiparous mothers are at a significantly increased risk of a SGA infant. The risk for the 2nd and 3rd pregnancies is non-significant. What is unexpected however, is the suggestion that the 2nd and 3rd pregnancies may be at a slightly lower risk than those mothers on their 4th or later pregnancy.

The Q-Q plot (Fig 5.12) shows a pattern along the lines expected. The primiparous mothers are at the highest risk and the risk decreases for the 2nd and 3rd pregnancies, though these two pregnancies seemed to be at a similar level and so were combined. The plot shows a slightly increased risk over the 2nd and 3rd pregnancies
for the 4th pregnancy and beyond, though this was not significant. Pregnancies beyond the 4th have been combined due to the small number of mothers in these categories.

In both the *a priori* ($\chi^2=21.30$, $p<0.001$) and Q-Q plot ($\chi^2=20.97$, $p<0.001$) situations the overall tests for differences between the groups are significant. The tests for linear trend are also significant in both situations ($\chi^2=9.034$, $p=0.00265$), and ($\chi^2=9.792$, $p=0.0018$) respectively. The differences between these $\chi^2=12.266$ and $\chi^2=11.178$ respectively both show that the linear component does not account for the overall differences seen between the groups.

Using the Q-Q plot categories with a binary outcome, the results are similar to the *a priori* results, the only difference being the combining of the 2nd and 3rd pregnancies.

Looking at birthweight produced results that were reasonably consistent with those from the binary outcome. In the *a priori* situation, the decrease in birthweight for primiparous mothers was significant, as expected. The decreases for the other pregnancies were almost nil, however. Whilst the odds ratios suggested that both the 2nd and 3rd pregnancies were at a slightly reduced risk than the 4th and later, there was in fact extremely little difference in birthweight for infants of multiparous mothers. Thus suggesting that all pregnancies other than the first, produce similar birthweight infants.

The categories suggested by the Q-Q plot were again consistent for the effect of primiparous mothers. The categories for 2nd and 3rd pregnancy combined showed no difference in birthweight compared to mothers on their 4th or later pregnancy.

Parity could be considered to be a continuous variable, though it does have a limited range and is in fact a count. Modelling parity as such, suggests that for each subsequent pregnancy, there is a 38.7 gram increase in birthweight. This is unlikely to be a suitable term to model given the above results and the tests for linear trend (Table 5.17). There is also unlikely to be an equal difference in risk between pregnancies.

It seems that it is more appropriate to categorise parity, than use it as a linear term in the model. The *a priori* and Q-Q plot categorisations both show that the only significant differences are in the primiparous group of mothers. The binary and continuous outcomes both seem consistent in this matter. In the long run it may be reasonable to combine all other parity categories. However the decision should be made in conjunction with the possibilities of interactions with maternal age.
Chapter 6: Multivariate Analysis of the National Study

This chapter considers the variables discussed in the previous chapter in a multivariate manner, i.e. controlling for associated factors.

The variables will be discussed in three situations; partial models, full model, and reduced model. First of all, models will be fitted using the \textit{a priori} and Q-Q plot categories within the variable groupings (referred to as partial models) as defined in the univariate case (Chapter 5). These partial models will be considered to determine the effects of the variables within each grouping on each other. Secondly, a full model will then be considered using all variables from each of the variable groupings. And thirdly, a reduced model will then be developed starting from the full model and moving in a "downwards" direction. This will be done by removing variables one at a time that do not have any significant direct effect on the outcome, and which show no signs of indirect effect (as determined by the change in parameter estimates of the remaining variables).

The analysis will consider both a binary and a continuous response.

In the tables provided for the partial models, the first column shows the univariate odds ratio or decrease in birthweight as determined in Chapter 5. The second column shows the effects after controlling for all other variables in the grouping of variables as defined in Chapter 5 (the partial model as described in Chapter 4), e.g. all other socio-demographic variables (maternal education, SES, marital status, and MSSI). The remaining columns show the effect on this partial model of removing from the partial model the variable indicated at the top of the column. The effects from the \textit{a priori} categories are shown in the top half of the table, using the binary then the continuous response, and similarly in the bottom half of the table using the Q-Q defined categories, where both have being considered. In the case where there was only an \textit{a priori} or a Q-Q category defined for a particular variable, these categories were used in both the \textit{a priori} and Q-Q plot models in relation to the other variables. These partial models will provide information for which the final decision will be made as to whether \textit{a priori} or Q-Q plot categories will be used in the full and reduced models.

The partial models using the variable groupings defined in Chapter 5 are:
1) Socio-demographic: socio-economic status, maternal education, marital status, and maternal social support.

2) Maternal lifestyle: maternal tobacco smoking, maternal marijuana usage, maternal alcohol consumption, and maternal caffeine consumption.

3) Genetic: ethnicity, maternal height, maternal weight, and maternal body mass index (BMI).

4) Obstetric: maternal age, urinary tract infection (UTI), antenatal care, multiple birth, and parity.

6.1 Partial Models

6.1.1 Socio-demographic Variables

6.1.1.1 Socio-economic Status

Using the a priori categories for SES (Table 6.1), the odds ratios, after controlling for other socio-demographic variables, are slightly changed from their univariate level. In the case of the middle socio-economic groups, the odds ratio has moved towards unity and is still not significant. The group for the lowest socio-economic status moves from close to unity, to a slight but still non-significant protective effect. Using a continuous response, the magnitude of the differences in birthweight in both the middle and low socio-economic groups is smaller than that in the univariate situation; both moving towards a null difference and becoming non-significant.

There is some inconsistency between the two analyses. Whilst the odds ratios for the lower socio-economic groups suggest a slight protective effect, the continuous response shows a decrease in birthweight, though neither the odds ratios nor the decreases in birthweight are significant. There is also no noticeable effect on socio-economic status when any of the other socio-demographic variables in the a priori situation are excluded from the model.

As in the univariate case, the Q-Q plot selected categories show a more detailed pattern than the a priori categories using a binary response. This pattern is not what would be expected (Table 6.1), however, none of
the odds ratio reach significance. As the univariate analysis suggested, those in SES group IV, are at a higher risk than the other groups. Using the continuous response, there is a similar result to the binary outcome with SES group IV having the largest decrease in birthweight, though this also does not reach significance. SES groups II and III, have a similar decrease to those in the lowest SES grouping. With these two groupings there is again an inconsistency as with the \textit{a priori} categories, in that, whilst the odds ratios suggest a slight protective effect, the continuous outcome suggests a decrease in birthweight. Though, like the odds ratios, none of these changes in birthweight reach significance.

Amongst the socio-demographic variables, there seems to be a small effect on socio-economic status caused by maternal education. This is most noticeable in the SES IV group where the point estimate of the odds ratio increases from $1.31$ to $1.52$ when maternal education is left out of the model. There are smaller changes towards unity in the other SES groupings when maternal education is excluded from the model. The decrease in birthweight, using the continuous response, changes most when maternal education is excluded from the model and is largest in the lowest SES groups. However, there is a general increase in the size of the decrease in all SES groupings, which is consistent to the movement seen with the odds ratios. None of these categories becomes significant.

Although the Q-Q plot categories show a little more pattern than the \textit{a priori} categories there remains no significant effect of socio-economic status after controlling for other socio-demographic variables using either method of categorisation, with either of the response variables. The Q-Q plot categories will be used in the final model as they have shown that SES III and IV should not be grouped together in this dataset.

\textbf{6.1.1.2 Maternal Education}

Odds ratios, after controlling for the other socio-demographic variables, have changed very little and are of borderline statistical significance (Table 6.2). There is no indication of the other socio-demographic variables having any effect on the \textit{a priori} categorisation of this variable. Similarly using a continuous response, there has been little change in the decrease of birthweights and no obvious effects from the other socio-demographic variables.

Using the Q-Q plot categories, there is little change in the odds ratio for those in the group who left school at the age of 15 or 16. However, there is a decrease from the univariate odds ratio for those in the group who left school before the age of 15. The numbers in this category (left before the age of 15) are small, hence the odds ratio is less stable (as can be seen from the relative size of the confidence interval). This seems to be
mainly due to confounding with the variable "marital status", as can be seen from the increase in the point estimate of the odds ratio from 2.34 to 2.62 for this category when the Q-Q categorisation for marital status is excluded from the model. Using a continuous response, the same situation occurs. The only changes in birthweight occurring in the partial model are for those less than 15 years of age when they left school. Again these estimates are less stable for this group (under 15) than for the other categories due to the smaller number of individuals in this category. Using a continuous response, the univariate decrease of 217g in the under 15 category has decreased to 158g. The effect of marital status is also consistent with that seen in the binary response case. Removing "marital status" from the model, changes the point estimate from a decrease of 158g to a decrease of 187g (Table 6.2).

In both the a priori and the Q-Q selected category situation, the odds ratios and the decreases in birthweight show a consistent pattern of risk. The only slight difference in consistency comes in the level of significance between the binary and continuous outcomes, the continuous response having smaller p-values than the binary response (probably due to the extra power that using a continuous response tends to give to the analysis).

The Q-Q plot selected categories show more pattern than those of the a priori categories after controlling for the other socio-demographic variables and will be the categories of choice for further analysis.

6.1.1.3 Marital Status

Marital status at the univariate level showed a significant risk of having a SGA infant for those mothers that were not married. When other socio-economic variables are controlled for, the odds ratio decreases slightly and the significance is lost. Similarly, using a continuous response, the size of the decrease in weight for babies of unmarried mothers becomes smaller and is no longer significant at the 5% level (Table 6.3).

The effects of the other socio-demographic variables on marital status in this a priori categorisation using the binary response are small and do not have any major effect. The largest effect comes from removing maternal social support from the model. In the case of the continuous response, excluding any of the other variables from the model is enough to make the decrease in birthweight for unmarried mothers significant at the 5% level, although there is very little change in the point estimate.

There are other ways of defining marital status as discussed in the univariate analysis in Chapter 5. The univariate analysis showed that mothers in de facto relationships were not different from mothers that were
married. The size of the risk of a SGA infant for single mothers was larger than that using the *a priori* category of married/unmarried. Controlling for the other socio-demographic variables as in the *a priori* case decreased the size and removed the significance of the odds ratio at the 5% level. Using the continuous response, there is a change in the decrease in birthweight, however it remains significant at the 5% level (Table 6.3).

The removal of either maternal education or maternal social support is enough to increase the odds ratio slightly and make it significant at the 5% level, though the changes in the point estimate are small. In the latter case this may suggest that being in some sort of relationship is an indicator of some maternal social support. As in the binary case, when using the continuous response, there is little difference in the size of the effects when each of the other variables are excluded from the model. There are slightly larger changes in the size of the point estimate when maternal education or maternal social support are excluded from the model, which is consistent with the binary situation.

The use of ‘single’ versus ‘being in a relationship’ seems to be a more appropriate categorisation than the *a priori* one of not being married, and hence will be used in the final model. Both methods of analysis give consistent results with this variable.

### 6.1.1.4 Maternal Social Support

The *a priori* categorisation for maternal support was created by using a cutoff that maximised the size of the odds ratio at the univariate level since there were no known predefined cutoff.

Using this categorisation, and controlling for the other socio-demographic variables, the odds ratio (like that of the other variables after controlling) decreased, the size of the effect remained significant at the 5% level. Using the continuous response, there is likewise a drop in the size of the decrease in birthweight, unlike the odds ratio the size of the effect is not quite significant at the 5% level. There is little effect in this model of any other individual variables on maternal social support. However leaving marital status out of the continuous response model is enough to increase the birthweight difference to a significant level (Table 6.4).

In the Q-Q plot model, the same categories were used for MSSI as in the *a priori* models, after the univariate analysis showed that there was no difference between the middle and high maternal social support score groups. Unlike the *a priori* model, the size of the odds ratio drops to a point where it is not quite significant
at the 5% level. Similarly, using a continuous response, the size of the effect of decrease in birthweight drops and is not significant, showing consistency between the results (Table 6.4).

The variable that has an effect on the significance of maternal social support when excluded from this model is marital status. Removing this variable from the model increases the odds ratio from 1.41 to 1.53 being significant at the 5% level. The size of the decrease in weight changes from 36g to 56g and also reaches significance. This confounding situation confirms that having some sort of relationship is an indicator of maternal support as well as suggesting the category single/other is more appropriate than married/unmarried.

As suggested by the univariate analysis, the *a priori* categories for MSSI will be used in further analysis.

### 6.1.2 Maternal Lifestyle Factors

Of the maternal lifestyle variables, both alcohol and caffeine consumption, had no *a priori* categorisation so therefore were categorised by Q-Q methods. Marijuana use was a simple yes/no variable and therefore did not require any other categorisation. The only variable that had both *a priori* and Q-Q categorisation was maternal smoking, the difference being a division of the 1-9 category into two categories of 1-4 and 5-9. As this is also a common *a priori* way of categorising smoking, the effect of this re-categorisation on the other variables is minimal and only the Q-Q analysis is presented.

#### 6.1.2.1 Maternal Smoking

After controlling for other maternal lifestyle variables, and using the binary response, the unusual pattern that existed in the univariate analysis with the odds ratios still continued, i.e. mothers who smoke 5-9 cigarettes per day are at a higher risk of SGA than those who smoke 10-19 cigarettes per day. The odds ratios in all the categories have decreased. However, all categories that were significant in the univariate analysis remained significant. Even though there is a strange pattern to the odds ratio, it is still evident that maternal smoking is a major risk factor for SGA with the risk most increased amongst the heavy smokers (Table 6.5).

With the decrease in odds ratios from the univariate level, there is obviously some confounding between smoking and other maternal lifestyle variables. This seems to be the case with marijuana use and maternal alcohol consumption. When marijuana use is removed from the model, the odds ratios for all the smoking categories increase by a similar proportional amount. This suggests that those who smoke marijuana are
distributed proportionally across the smoking groups and that marijuana is a partial confounder. In the case of maternal alcohol being removed from the model, the change in the heavy smoking group is noticeably larger than that for the lighter smoking groups. This suggests that the heavy drinkers are also likely to be the heavier smokers. Removal of maternal caffeine intake from the model has very little effect on the smoking odds ratios.

Using the continuous response, as in the binary case, the unusual pattern at the univariate level continues, i.e. the 5-9 group has a larger decrease in birthweight than the 10-19 group. The only association that seems to take place with the other variables however is a small increase in the reduction in birthweight across all the smoking categories when marijuana use is removed from the models. This is reasonably consistent with the effect that was seen using the binary response (Table 6.5).

### 6.1.2.2 Maternal Marijuana Use

Using the binary response for this simple yes/no variable and controlling for the other maternal lifestyle variables, there was a marked decrease in the size of the odds ratio. However it remained significant at the 5% level (Table 6.6). It was expected that there would be a large effect from smoking on this variable since it is known that nearly all the marijuana smokers also smoked tobacco. What the significant odds ratio shows is that smoking marijuana has an effect additional to smoking just tobacco. When the effects of the removal of the variables in the model are looked at, the only real noticeable change is when maternal tobacco smoking is excluded from the model. The point estimate of the odds ratio increasing from 1.81 to 2.35.

Using the continuous response shows a very similar pattern, in that, when these other variables are controlled for, there is an almost halving of the size of the decrease in birthweight from smoking marijuana, and this reached significance only at the 6% level (Table 6.6). Similar to the binary outcome, there was very little change to the decrease in birthweight from marijuana smoking when maternal caffeine consumption or maternal alcohol consumption were excluded from the model. The only major change occurred when maternal tobacco smoking was excluded from the model. This, as one would expect, increased the size of the decrease considerably from 90g to 162g.
6.1.2.3 Maternal Alcohol Consumption in First Trimester

As was noted previously, the categories for maternal alcohol consumption were chosen by Q-Q methods. The notable changes that take place when other maternal lifestyle variables are controlled for, is that the effect at the univariate level for moderate drinkers moves in the protective direction, though is still not significant at the 5% level. The odds ratio for the heavy drinkers however moves towards the null, and although not quite significant, is still in the direction of risk. The most noticeable thing about the group of moderate drinkers when each of the other maternal lifestyle variables is excluded from the model, is that there is almost no effect. With the heavy drinkers, however, there is little change when maternal caffeine consumption is removed from the model. This group is affected by the removal of maternal smoking of both tobacco and marijuana from the model (Table 6.7).

For marijuana usage, the point estimate for the odds ratio increases from 1.59 to 1.75. The change in the odds ratio when maternal tobacco smoking is excluded from the model is similar, the odds ratio increasing to 1.83. Removal of either of these variables from the model makes the estimates of risk for the heaviest drinkers significant at the 5% level.

Using the continuous response shows a pattern that is consistent with that found with the binary response. When the other maternal lifestyle variables are controlled for, the size of the increase in birthweight for the group of moderate drinkers is larger, though not quite significant at the 5% level. The size of the decrease in birthweight for the heavy drinkers is smaller than at the univariate level, but is still significant. Like the binary situation, removal of other variables individually had little effect amongst the group of moderate drinkers. The removal of marijuana use or caffeine consumption from the model increases the size of the decrease in birthweight for the heavy drinkers. However the largest effect is reserved for that from maternal tobacco smoking. When tobacco smoking is excluded from the model the magnitude of the decrease in weight changes from 82g to 118g (Table 6.7).

These consistent results from both the binary and continuous response suggest a slight protective effect (increase of birthweight) in those infants of mothers who drink alcohol in moderation, and show a risk for those who are heavy drinkers. It should also be noted that since alcohol has an effect on the heavy smoking category, smoking in turn has an effect on the heavy drinking category.
6.1.2.4 Maternal Caffeine Consumption in First Trimester

Like the categories for maternal alcohol consumption, those for caffeine consumption were chosen using Q-Q methods. The univariate odds ratios for caffeine consumption suggested a possible dose-response relationship, although neither the moderate nor heavy coffee drinkers were at a significantly increased risk and a test for linear trend was not significant. This is no longer the case when the other maternal lifestyle variables are controlled for, with both the heavy consumers and the moderate consumers having odds ratios only slightly above unity. The only change of any note when considering the relationship of the other maternal lifestyle variables to caffeine consumption is when tobacco smoking is excluded from the model. In this situation, the odds ratios for both groups are raised and the odds ratio for the heavy consumers is greater than that for the moderate consumers, though still not significant (Table 6.8).

Using the continuous response, significant decreases in birthweight at the univariate level become smaller and non-significant after the other variables have being controlled for. Again, similar to the binary case is the effect of the exclusion of other maternal lifestyle variables from the model. The only effect of any note is when tobacco smoking is removed from the model, i.e. the decrease in birthweight for the moderate consumers is of greater magnitude, although not quite significant. For heavy consumers the decrease in weight is much larger and reaches significance at the 5% level (Table 6.8).

The effects between maternal caffeine consumption and other lifestyle variables are similar to those of maternal alcohol consumption and tobacco smoking. The effects on categories of caffeine consumption by other lifestyle variables occur only in the heaviest category of caffeine consumption and only with tobacco smoking.

6.1.3 Genetic Factors

6.1.3.1 Ethnic Group

The categories for this variables are naturally the same in both the a priori and the Q-Q model as they are distinct ethnic groups that it would be inappropriate to combine when looking for possible ethnic differences in birthweight and risks of SGA infants.
Even though Maori and Pacific Islanders are genetically similar, the partial model that controls for maternal height, weight and maternal body mass index (BMI) (Table 6.9), shows why the two ethnic groups should not be combined. When these factors are controlled for, there is a slight increase in the odds ratios for Maori. However, the odds ratio for Pacific Islanders moves from slightly protective to a similar level to that of Maori. Although it is non-significant, this is mainly due to the numbers in this group being relatively small (Table 6.9).

Using the continuous outcome, and controlling for these factors, leaves the decrease in birthweight for the Maori group similar to that in the univariate case. However the change in birthweight for the Pacific Island group changes from a significant increase in the univariate case, to a slight non-significant decrease after controlling for this group of variables.

The effects of the other variables in the *a priori* and Q-Q situations on ethnic groups are moderate and similar in size. In the case of maternal height, there is little difference in the odds ratio or the decrease in birthweight. The effect of maternal weight shows a small increase in the odds ratios for the Pacific Island group using the Q-Q categories. Using the continuous response, the size of the decrease in birthweight for the Pacific Island group becomes smaller. There are no changes in odds ratios or changes in birthweight for the Maori group. Removing BMI from the model has no effect on the odds ratios or the birthweight difference.

These maternal characteristics seem to have an effect on ethnic group, particularly on the Pacific Island group. The size of effect due to Maori ethnicity stays at a similar level to the univariate effect. The models showed consistent results for the Maori group with the two responses. Those produced in the Pacific Island group are not as consistent with the odds ratio similar to the Maori risk but the birthweight decrease being much smaller.

The *a priori* categories will be used in the final model.

### 6.1.3.2 Maternal Height

Using the *a priori* categories for maternal height and controlling for ethnic group, maternal weight, and maternal BMI, there is a small increase in the size of the odds ratio for those in the “short” group, and a slight decrease for those in the “tall” group. When the other variables are removed from the model, we see amongst the short group an increase in the odds ratio if maternal weight is removed, and a slightly larger decrease if
BMI is removed. There is an increase in the odds ratio to the univariate level in the tall group when BMI is removed (Table 6.10).

Using a continuous response makes little difference to the point estimates of the changes in birthweight, though the estimates for both groups move towards 0. The effect of maternal weight on these groupings is much the same for the "short" group as in the binary response case, i.e. an increase in the decrease of birthweight for the "short" group, and an increase in the magnitude of the birthweight difference amongst the "tall" group. Similarly, by removing BMI there is a decrease in the size of the birthweight difference amongst both groups.

The Q-Q plot categories also contained three groups and were only slightly modified from the original boundaries that had been chosen in the \textit{a priori} case. As in the \textit{a priori} situation, after controlling for ethnic group, maternal weight, and maternal BMI, the odds ratios for the groups moved further from unity. The odds ratios for the "short" and "tall" groups being of similar magnitude but in opposite directions. Also as in the \textit{a priori} case, the effects of removing maternal weight or BMI are similar and mainly in the "short" group.

Using the continuous response, and controlling for the other variables, there is again a small decrease in the magnitude of the differences in birthweight for the "short" and "tall" groups, as in the \textit{a priori} case. Again, the effects of maternal weight and maternal BMI are like the \textit{a priori} case (i.e. there is a large decrease in birthweight for the "short", and increase in birthweight for the "tall" group), as opposed to only the short group when using the binary outcome.

### 6.1.3.3 Maternal Weight

The \textit{a priori} categories for maternal weight are affected more by controlling for the other variables than those of maternal height. The category for the women of the lowest weight has a decrease in the odds ratio and becomes non-significant. The category for the heavier women has an odds ratio that changes from slightly protective to a slight risk and remains non-significant. The odds ratios for maternal weight are only markedly affected by the absence of maternal height or BMI in the model. The removal of either of these variables results in a marked increase in the odds ratio for the "light" group and a return to the univariate level for the "heavy" group (Table 6.11).
Using the continuous response, after controlling for other variables, there were decreases in the magnitude of the changes in birthweight apparent amongst both groups. The effects of the other variables on the maternal weight are as in the binary case, i.e. the effects of removing maternal height or BMI producing results that are similar in size and direction to the binary situation.

The Q-Q categories like the \textit{a priori} categories show that controlling for the other variables creates most change in the lightest categories, with a decrease in the odds ratio for the lightest group from 3.99 to 1.56, and a smaller decrease in the odds ratio for the next lightest group. Smaller changes occur in the groups containing the heavier women. Likewise, these natural categories are also altered in their status by the other variables in the model. Hence, the changes when maternal height or BMI is removed from the model are quite large in the lightest category, and of reasonable size in the next lightest category. The effects of maternal height or BMI being removed are similar to those seen using the \textit{a priori} categories.

Using the continuous response again showed consistent patterns and changes when variables are removed from the model.

\textbf{6.1.3.4 Maternal Body Mass Index}

The effects of maternal height and maternal weight on each other in these models highlights the absolute necessity to have both of these variables in the model, or to have some combination of the two. This is the purpose of the maternal body mass index, i.e. a combination of maternal height and weight.

The categories were determined by Q-Q plot as there was no known \textit{a priori} categorisation for this variable in relation to women prior to pregnancy. Therefore the categories broadly refer to "light for height", "average" and "heavy for height". These three categories were used along with both the \textit{a priori} and Q-Q categories for maternal height and weight.

When this variable is placed in the model with ethnic group, maternal height, and maternal weight in the binary response situation, there are only small changes from the univariate odds ratio. Using the continuous response, the magnitude of the changes in birthweight are larger than those expected from what was seen using the binary outcome in the low BMI group. The results are similar for both the \textit{a priori} and Q-Q models (Table 6.12).
As in the case of maternal height and weight, there is little effect on BMI when ethnicity is removed from the model. Removing maternal height from the model moves the odds ratios towards unity in both the "light for height" and "heavy for height" categories. This change is a little inconsistent for the "heavy for height" group in the Q-Q model where the protective direction turns to risk. Using the continuous outcomes also shows movement towards unity of the decreases in birthweight, again with the same exception.

Removing maternal weight from the model has the largest effect with an increase in the odds ratio for the "light for height" group, although little change in the "heavy for height" group. These changes are more notable using a continuous outcome with the magnitude of the effects on birthweight doubling in both the a priori situation, and the Q-Q situation.

After consideration of maternal height, weight, and BMI, the use of all three seems to overfit the model and the model becomes confusing. Using just BMI does not adequately describe all that is going on with height and weight, so Q-Q plot categories for maternal height and weight will be used in further analyses.

### 6.1.4 Obstetric Variables

#### 6.1.4.1 Maternal Age

Maternal age showed very little effect at the univariate level using either a priori or Q-Q plot categories. This lack of pattern continues after controlling for the other obstetric related variables. Using the group "mothers 30 years of age or older" as the base category, those in the groups for 20-24 and 25-29 both give a point estimate for the odds ratio near unity. The odds ratio for those less than 20 is in the protective direction but not significant. Using a continuous response shows very little difference in birthweight of any the groups. The birthweight difference for the less than 20 year olds however is in the opposite direction to that of the odds ratio (Table 6.13).

The variable that does have an effect on maternal age is parity. Leaving parity out of the model increases the risk in both the 20-24 and the 25-29 age groups but not to a point of significance. The largest change is in the group of mothers less than age 20. This group changes from a non-significant protective effect to a slight non-significant risk. Using the continuous response, the decrease in birthweight for the 20-24 and 25-29 year old groups increases, but not quite to significance, at the 5% level. However the decrease in birthweight for
those less than 20 returns to the univariate level, which suggests confounding between parity and young maternal age.

The effects of the other obstetric variables on maternal age using the Q-Q analysis categories of parity and antenatal care were very similar, with parity having the only and almost identical effect (Table 6.13).

These models show that maternal age appears to have very little effect after controlling for other obstetric variables, but is intertwined with the effect of parity. The groups for 20-24 and 25-29 year olds seem to be very similar and could be collapsed but it seems reasonable to leave these groups separate due to their size and the effect that some of the non-obstetric variables may have on maternal age.

6.1.4.2 Urinary Tract Infection (UTI)

This variable is naturally the same in both the *a priori* and the Q-Q models since it is a simple yes/no variable. After controlling for the other obstetric related variables, the odds ratio decreases and thus remains non-significant. Removal of other obstetric variables from the model showed no effect except for when antenatal care is removed from the model. In this situation the odds ratio increases (though remains non-significant) (Table 6.14).

Using a continuous response, there is a decrease in the birthweight difference from the univariate level when the other variables are controlled for. However, the decrease in birthweight is not significant, possibly due in part to the small numbers who actually have a UTI. As in the binary case, the only noticeable change in the decrease in birthweight is when antenatal care is not controlled for, and the reduction increases in size but is still not significant at the 5% level.

In the models containing Q-Q selected categories the odds ratios and decreases in birthweight are almost identical.

6.1.4.3 Antenatal Care

In the *a priori* situation, this variable was simply divided into early and late antenatal care dependent on when the first antenatal attendance took place. When the other obstetric variables are controlled for, there is little change in the odds ratio for the risk of late antenatal care (Table 6.15). Using the continuous response, the
result after controlling is consistent with that of the binary response with little change in the decrease in birthweight.

When the effects of the other obstetric variables on time of first antenatal care are considered, the only change that appears to take place is when parity is excluded from the model. This produces a decreased odds ratio which remains significant at the 5% level. Consistently, when the continuous response is used, the only time there is a change in the size of the decrease in birthweight, is when parity is removed from the model. The size of the decrease is smaller, but significant, and seems consistent with that shown with the binary response.

The Q-Q plot categories were chosen at the univariate level in such a way that they reflected a much greater pattern in the time of the first antenatal visit. When the other obstetric variables were controlled for, and a binary response used, there was a slight increase in the odds ratio for the two groups of later antenatal attenders. The dose-response type pattern for the later attenders at the univariate level is still present, and the much higher risk still present for those who attended at 0 months. Similarly, as when the a priori groups were used, there was a small decrease in the odds ratios for the latest attenders when parity was excluded from the model. However, the odds ratio increased for those very early attenders, although this estimate is unstable due to the small numbers in this group (Table 6.15).

As in the univariate analysis, the results using the Q-Q plot categories with the continuous response are inconsistent with the results produced from the binary response. When the other obstetric variables are controlled for, there is no significant difference between the very early attenders and those that attended in the 2nd or 3rd months of pregnancy or in the first month of pregnancy. Collapsing these categories of course would put us back in the a priori situation. Looking at the effects of the other variables on this categorisation, the only change in the size of the birthweight decrease is when parity is excluded from the model, for those in the group of late attenders and very early attenders.

It seems that the pattern observed at the univariate level is inconsistent between the binary and continuous response. The pattern only seems to exist with the binary response, which is natural since it is from this response that the categories were derived. Given that the continuous model is more powerful, and is the true outcome, the a priori categories will be used in the full model.

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6.1.4.4 Multiple Birth

Multiple birth is a simple yes/no variable and has the same *a priori* and Q-Q categories. After controlling for other obstetric variables, the odds ratios and change in birthweight increase from the already high levels (Table 6.16). The model removing maternal age showed little difference to that when all obstetric variables were controlled for. In both the *a priori* and Q-Q models, removing parity and antenatal care from the model decreased the odds ratio and reduced the change in birthweight to a similar level to those of the univariate estimates. In the case of leaving UTI out of the model, the odds ratio and decrease in birthweight actually increased.

As one would expect, being a twin has a marked effect on birthweight and, hence, also the risk of being below the 10th percentile. As mentioned in Chapter 5 though, the percentile curves also contain multiple births and, hence, multiple births were left in the dataset with an indicator variable placed in the model.

6.1.4.5 Parity

Using the *a priori* categories for parity, the effect of primiparity is even greater after controlling for potential confounders than at the univariate level. The point estimate of the odds ratio increased from 1.71 to 2.22. The slight, but non-significant, protective odds ratios for 2nd and 3rd pregnancy groups are still present but the point estimates have moved towards unity (Table 6.17).

Looking at the effects of the other obstetric variables on parity, there seems to be a small effect of maternal age, but only in the group of primiparous mothers where the odds ratio decreases slightly. The odds ratios for the other groups stay much the same. The other variable that has an effect on parity is antenatal care. Removing antenatal care from the model decreases the odds ratios in all the parity groups to a similar level as seen in the univariate analysis.

Using the continuous response, the effect of a primiparous delivery has also increased after controlling for the other obstetric factors, i.e. the decrease in birthweight increasing from 152g to 173g. The discrepancy that was seen at the univariate level between the binary and continuous response for the 2nd and 3rd pregnancies also continues. The model suggests a decrease in the birthweight for the infants that are second or third born in comparison to those with greater parity using the continuous response, and a protective effect using the binary response. However, these differences in birthweight and risk are small and not significant.
Unlike the binary response, there is very little change in the effect of parity when maternal age is removed from the model. There is, however, a similar effect to the binary outcome when antenatal care is removed from the model with the decreases in birthweight moving close to those from the univariate analysis.

The Q-Q categories for parity are naturally similar to the a priori situation except that the groups for 2nd and 3rd pregnancy have been joined due to their similarity at the univariate level. With so little change to the categorisation, there is no difference in the pattern of the odds ratios from the a priori situation. Therefore primiparous mothers are at an increased risk of having an SGA infant, and those in the combined group show a slightly protective effect (Table 6.17). Again the effect of other obstetric variables on parity is similar with a slight decrease in the odds ratio of primiparous mothers when maternal age is not controlled for, and a decrease in the odds ratios when antenatal care is not controlled for.

Using the continuous response with the Q-Q categories produces an almost identical response to the a priori situation. The same discrepancy in direction between the odds ratio and the continuous response is evident, as well as the same effects of other obstetric variables.

The Q-Q categories will be used in the full model as the point estimates for the 2nd and 3rd pregnancies are similar.

6.2 Full Model

The full model was fitted by putting the four groups of variables previously discussed in a model together, thus controlling for all factors that had been considered. Controlling for all these variables removes (as much as possible) the effects of confounding between factors that may be in different groups. The variables will be discussed in their previous groupings below. This analysis was carried out using both outcomes to check for consistency in confounding between the two.

6.2.1 Socio-demographic Variables

Using the binary response, the indicator variables for maternal education show no relationship to the outcome, with the point estimates for the odds ratios not large (Table 6.18). Likewise, the effect due to marital status and maternal social support are small and non-significant. The model shows a decreased risk of
a SGA infant for the socio-economic groups containing SES II and III, and for the lowest SES group, compared to the highest SES group. The SES IV group previously at highest risk, shows an effect in the protective direction but is not significant.

Likewise, using the continuous outcome, there is no increased risk of a SGA infant for the maternal education indicators, although the point estimate for the lowest maternal educational group is relatively large. Again, the effects for marital status and maternal social support are small and non significant (Table 6.18). The main discrepancy in the two outcomes lies in the socio-economic status variable, the continuous outcome showing only small non-significant changes in birthweight across the SES groupings.

There has been little change in effect from the socio-demographic variables in the partial models to this full model with the exception of; an increase in significance amongst the SES groupings using the binary outcomes, and, a decrease in the change in birthweight to a non-significant level for being single.

6.2.2 Maternal Lifestyle Factors

Using the binary outcome, the effect of maternal smoking continues and in general is increased over that seen in the partial model. The unusual pattern continues and remains unexplained. The risk from smoking marijuana is decreased and not-significant. There is still no effect of maternal caffeine consumption or maternal alcohol consumption, though the risk for "moderate" drinkers has decreased and is approaching significance (Table 6.19).

Using the continuous outcome, the effect of maternal smoking continues, although, unlike the binary case, the point estimates have decreased a little, being for the smokers of 5-9 cigarettes per day now similar to those that smoke 10-19 cigarettes per day. The effect due to marijuana smoking is also decreased although the point estimate is still of a reasonable size. As with the binary response, there are no significant effects due to caffeine consumption or alcohol consumption though the relationships are interesting. The point estimate for the "heavy" caffeine consumption group shows a reasonable decrease in birthweight, whilst the point estimates for "moderate" and "heavy" alcohol consumption are of reasonable size, showing increases and decreases in birthweight respectively, with the effect in "moderate" drinkers again approaching significance (Table 6.19).

Exposure to tobacco remains the main variable of risk amongst this group of variables. However, the other variables show interesting trends.
6.2.3 Genetic Factors

Considering the outcome as a binary variable, the effects due to ethnicity have now disappeared after controlling for all the other variables. The effects of maternal height are very similar to those seen in the partial model situation without maternal BMI, which are still significant and show a quadratic like effect. Also, the effects due to maternal weight show a similar pattern to this partial model though the risk for the lighter women is slightly smaller than in the partial model and for the 51-58 kg group is also significant at the 5% level (Table 6.20).

Considering birthweight continuously, as in the binary situation, after controlling for all the other variables, there is no apparent effect due to ethnicity. Also, the changes in birthweight for the maternal height groupings are very similar to those seen in the partial model after maternal BMI was removed. The magnitude in birthweight changes amongst the maternal weight categories have decreased for the lighter women, and the 51-58 kg group is not significant at the 5% level. The changes in birthweight are almost the same for the groups of heavier women and remain significant, both being of similar magnitude (Table 6.20).

The binary and continuous outcomes show very consistent results amongst this grouping of variables, including the magnitude of changes associated with the removal of variables from the model. Both maternal height and weight are notably important in relation to birthweight.

6.2.4 Obstetric Variables

Using the binary outcome, the protective effect for young mothers has become significant. Although there is still no significant effect from the other maternal age groups, there is a steady trend towards unity up through the age categories. Also, the risk for first borns has increased, but this may be associated with maternal age since younger mothers are more likely to be on their first pregnancy. Again, there is no difference between other parities. There is also a continuing increased risk due to late antenatal care. There is no effect due to a urinary tract infection. Multiple births show an increased risk as in the univariate situation though the confidence interval was considerably wider suggesting the estimate has low validity. This risk also seems to have increased in size (Table 6.21).
Similarly, using the continuous outcome, there is now an increased birthweight associated with young maternal age. This is significant for the two youngest maternal age categories and was not seen in the partial models. This again seems to be associated with the decrease in birthweight for primiparous mothers. However, there is also a notable decrease in birthweight for those mothers of parity 1 and 2, though not quite significant at the 5% level. The decrease in birthweight associated with late antenatal care is also not significant at the 5% level, though the point estimate is of a reasonable size. Again, there is no effect due to a urinary tract infection. The decrease in birthweight continues for those infants that were twins. However, the magnitude of the change in birthweight is unchanged from the univariate level unlike the odds ratio in the binary situation (Table 6.21).

The effects of the obstetric variables are still of a similar nature to that seen in the univariate and partial models. Maternal age and parity are of obvious importance in regard to birthweight and are correlated to a reasonable extent, hence the intertwined effects that seem to be present.

Analysis of the residuals from the multiple linear regression showed that they were normally distributed with a standard deviation of 415.1041. A test was performed for normality using proc univariate in SAS, this produced a Shapiro-Wilk statistic of 0.988714 with a p-value of 0.7669, showing that the residuals are very well fitted by the normal distribution.

6.3 Reduced Models

The full models were reduced starting from the models described above. Variables were removed from the model one by one to ensure they did not have any major effects on the estimates of other variables due to confounding. Some variables were retained in models even though they did not show significance if the point estimate was large and the lack of significance was likely to be due to small numbers. Some variables will also have categories combined due to there being no difference between the categories concerned. The models arrived at using the binary outcome and the continuous outcome can be seen in Tables 6.18 to 6.21.

6.3.1 Binary Outcome

Using the logistic model, variables were removed that did not show any significant relationship to the outcome. Also some adjoining categories of other variables were combined due to there being no difference between the groups. The first three variables, removed one at a time, were; the indicator for single versus married or defacto relationship, the indicator for urinary tract infection, and the variables relating to caffeine
intake. These three variables (as can be seen from the odds ratios in the full model) had point estimates close to unity. Removal from the model had little effect on the other variables in the model, hence there seems little point in retaining them. The effect of the mother’s relationship had already been decreased by other socio-demographic variables. Urinary tract infection never showed any association with the outcome. And any effect of maternal caffeine use was overwhelmed by the effect of maternal smoking.

The next variables removed were those indicating Maori and Pacific Island ethnicity. The univariate model had shown an increased risk amongst Maori, which increased slightly after controlling for maternal height and weight. The risk for Pacific Islanders was also at a similar level to that for Maori after controlling for maternal height and weight. In the full model, the increased risks are small and non-significant. The reduction in these risks is likely to be due to controlling for socio-economic variables and maternal smoking. The removal had little effect on any of these factors. This suggests that any increased risk amongst Maori and Pacific Island mothers of a SGA infant is not due to ethnicity.

The next adjustments to the model involved cutting down some redundant categories. These included; "heavy" maternal weight which no longer showed any real protective effect, the 25-29 year old mothers were not different in risk to the 30+ year olds, and those with 1 and 2 previous pregnancies showed no difference to those that had 3 or more pregnancies. Maternal age and parity have noticeably been highly related to each other, hence it was a little surprising that reduction of the categories had little effect on the parameter estimates of the other categories. This suggests that most of the fluctuating relationship between these variables lies in the mothers of young maternal age and high parity, of which there are few in number.

The next variables removed from the model were those that were an indicator of maternal social support and marijuana usage. Both these variables showed slight increased risks in the full model after having shown significantly increased risks at the univariate levels. In the case of maternal social support, the decrease in risk seems, from the partial models, due to the other socio-demographic variables, not just from the relationship status of the mother. In the case of marijuana usage, the decrease in risk is mainly due to controlling for maternal smoking of tobacco.

The final variables removed from the logistic model were “age mother left school” and alcohol consumption. The age mother left school was significant at the univariate level and after controlling for the other socio-demographic variables. However, after controlling for the rest of the variables in the model the size of the effect is reduced to a small, non-significant one. Alcohol consumption does not show any significant effect
even though the risk for the moderate drinkers has tended towards protection and that of heavy drinkers towards risk.

The -2 log likelihood for the full model was 666.358 (38 d.f). After model reduction, this has increased to 692.019 (18 d.f). Normally a Chi-squared test can be carried out to test that there is no significant decrease in the adequacy of this reduced model. Unfortunately because of the way in which SAS works the models have been fitted using different numbers of observations. This is due to the fact that removal of insignificant variables from the model has decreased the number of observations with missing data. Hence tests to check for any decrease in the adequacy of the model have not been carried out.

### 6.3.2 Continuous Outcome

Using birthweight in its natural form and modelling the data using all the variables also produced a model in which some variables seemed redundant.

As in the binary model, the socio-demographic variables showed little effect on birthweight after controlling for the other variables. The first variables removed from the continuous model in the reduction process were; socio-economic status, maternal social support, and urinary tract infection. Socio-economic status was the only socio-demographic variable left in the binary model after reduction was complete and is, notably, the first variable to be removed from the continuous model. This, to some extent, shows how closely related the socio-demographic variables are in relation to birthweight.

Maternal social support was the next variable removed, whereas in the binary model the variable relating to the mothers marital status (which seem to be closely related) was removed early. Again, as in the binary model, UTI showed no relationship to birthweight.

The next variable to be removed from the model was ethnicity. As in the binary situation, controlling for maternal height and weight removed any effect of Pacific Island ethnicity, though Maori ethnicity remained at a significantly decreased birthweight. After controlling for other variables however, all effects due to ethnicity disappeared, this seems likely to be due to controlling for maternal smoking.

The next process in the reduction of the model was to reduce the number of categories for maternal age. As seen in the binary situation, the 25-29 year old age group showed no difference from the 30+ age group. Again, this emphasises that the relationship between maternal age and parity is likely to lie amongst the young
mothers of high parity. There was also no difference between those that left school at 15 or 16 years of age and those that left school when they were older than 16.

A number of other variables remained non-significant in relation to birthweight. These variables, though, have reasonably sized changes in birthweight associated with them. Such variables were, marijuana usage (which has been much reduced in its effect on birthweight, due to control of confounding with maternal smoking), and mother's marital status (which also showed no significant effect even though the point estimate showed a change of more than 40g). Even more notable was the lack of significance for those that left school at less than 15 years of age, even though the point estimate showed a decrease of nearly 100g in birthweight. This is likely to be due to the small numbers of mothers that fall into this category (Table 6.18).

The models show overall fits that went from an r-square of 0.2874 for the full model, to an r-square of 0.2841 for the reduced model. Testing to check for the adequacy of the model can be done with an F-test. However, testing whether the subset of parameters fitted the model equally well has the same problem as in the binary model, in that the full and reduced models have different numbers of observations.

The retention in the model of variables that are non-significant but showed reasonable sized changes in birthweight, is open to debate. However, the lack of significance amongst most of these variables is likely to be due to small numbers in some of the cells, so it seems best to retain them in the model as a matter of precaution.

6.3.3 Comparison of Binary and Continuous Models

The binary and continuous outcome models are not entirely consistent in the variables that best predict the outcome. However, though the models do differ in the variables that are significantly related to the outcome the variables that differ in the two models are related. In these situations, the relationship to the outcome of these variables is likely to be an indirect one as in the case of socio-demographic variables.

In both models, the variables that have most effect of the outcome are the same. These are: maternal age, parity, maternal smoking and, to a slightly lesser extent, antenatal care, maternal height, and maternal weight.

Another way of comparing the manner in which the independent variables are associated to the two outcomes is to look at the relationships of the odds ratios and the decreases in birthweight. For ease of comparison, it is easiest to look at the full model. A plot of the odds ratios against the decrease in birthweight
shows a general increase in the magnitude of the decrease in birthweight with increasing odds ratios (Fig 6.1). A model of the odds ratio predicted by the change in birthweight gives a model of Weight Change = -80.84*OR. The point for multiple birth is well away from the other points due to its size. When the point for multiple birth is removed the model becomes Weight Change = -93.5*OR. Hence a unit increase in the odds ratio is approximately equal to a 100g decrease in birthweight, with an odds ratio of 1 being equivalent to no change in birthweight. So, for example, an odds ratio of 2 is equivalent to a decrease in birthweight of 100g. Hence the models seem to be consistent in their prediction, especially among variables that are directly related to the outcome.

6.3.4 Issues of Multiple Comparisons

As described in chapter 4, the use of Q-Q plots to determine where continuous variables should be split in order to determine categories, brings to light the issue of multiple comparisons. As described earlier, whether and how this should be done is a matter of contention. Tables 6.22 and 6.23 show the p values of the variables contained in the reduced models for the binary and continuous outcomes respectively. As can be seen from these tables, those variables that are significant at the 5% level are, in general, highly significant and, hence, remain significant even when we make a correction for the multiple comparisons.
Chapter 7: Univariate Analysis of National Womens Data

The data from this dataset has been considered in the same manner as that of the data from the NZCDS dataset in Chapters 5 and 6. The larger numbers of subjects (n=7227) allowed infants below the 3rd percentile to be considered as a separate group. Hence the analysis compares those infants below the 3rd percentile, and those between the 3rd and 10th percentiles, separately from infants whose birthweight was on or above the 10th percentile. This allows comparison to see which is the better cutoff in determining SGA. It also allows investigation into whether there is a difference between these two groups of small infants. The data is also considered using birthweight as a continuous variable.

A number of the variables in this dataset are the same as those in the NZCDS dataset, which will allow comparison to see if the risk factors have similar sized effects. In addition, some extra variables not contained in the NZCDS dataset are available on this dataset, which may allow further insights into factors associated with SGA and birthweight.

Using the percentiles defined in Chapter 2, it was found that 168 (2.3%) were below the 3rd percentile and a further 413 (5.7%) were between the 3rd and 10th percentiles. This suggests one or a combination of the following: 1) Birthweights have increased slightly since the percentiles were produced, 2) Term infants born at National Womens Hospital have slightly heavier birthweights than for the country as a whole.

Where variables are of a continuous nature and available for exploratory analysis, Quantile-Quantile plots were produced using the 10th percentile as the cutoff between cases and controls. This was done to obtain greater numbers, thus giving more stability in the nature of the curves and their relationship to the outcome. This also allows comparison for some variables with Q-Q plots produced in Chapter 5 with the NZCDS dataset. Variables that were already of a categorical nature were not considered in this way as they were already in broad categories in the dataset.

This analysis uses information on all births in 1992 on a defined population, i.e. women who booked and delivered at National Womens Hospital. The measurement of risk being used in the following two chapters will be that of the odds ratio as used in the previous chapter with the NZCDS sample.
7.1 Variables Used in Percentile Definitions

7.1.1 Gestation

Odds ratios for gestation show no significant increases in risk and confirms that there are no significant differences between the three percentile groups in the distribution of gestation (Table 7.1). As noted in Chapter 4, the univariate analysis using the binary outcomes will not control for gestation as this has in effect been done by the definition of the SGA groups using the percentile curves. Using birthweight as a continuous outcome shows the expected increasing weight with increasing gestation, hence the need to control for gestation when the continuous outcome is used. Furthermore, other factors may also have an effect on gestation as well as birthweight.

7.1.2 Infant Sex

As one would expect, when using sex specific birthweight percentiles there was no significant increase in risk of either gender, though the odds ratio was slightly above unity for males in comparison to females. Using birthweight as a continuous outcome shows that female infants are on average 137g lighter than males (Table 7.1), which is similar to that reported by Kramer\textsuperscript{120} of 126.4g in developed countries. In comparison, the difference in the data used to define sex specific percentiles in Chapter 2 was 112.5g. Sex will not be controlled for in univariate analyses when using the continuous outcome as sex should not affect the relationships of birthweight with the factor of interest.

7.2 Socio-Demographic Variables

7.2.1 Booking Trimester

The greatest proportion of women booked for delivery during the second trimester of pregnancy. When the percentile cutoffs are used, the odds ratios (Table 7.2) show a decreased risk of having an infant below the 3rd percentile for those who booked the hospital within the second trimester of pregnancy, compared to the first trimester. There were no other differences due to booking trimester using the binary outcomes. Using
birthweight continuously booking trimester does not show any significant change in birthweight associated with booking trimester, and the trends are consistent with those of the odds ratios.

Booking trimester does not appear to have any major effect on birthweight. The only difference identified is a slightly decreased risk of being below the 3rd percentile amongst the group booking in the second trimester.

7.2.2 Geographical Area

National Womens Hospital is the main place of birth for women in the central Auckland area, though the hospital also takes deliveries from women who reside in south Auckland and to a lesser extent on the North Shore. There are also a small number of women from outside the Auckland area who deliver at NWH. Women from other parts of the country have been excluded from this analysis due to a zero cell for the 3rd to 10th percentile group and only 2 being below the 3rd percentile. These observations have also being discarded from further analyses.

The risk for being below the 3rd percentile and for being between the 3rd and 10th percentiles did not vary between the three geographical areas- central Auckland, south Auckland and North Shore. Using birthweight continuously also showed no significant differences between the mother’s area of residence (Table 7.2).

7.2.3 Marital Status

Infants of single mothers have an increased risk of being below the 3rd percentile or between the 3rd and 10th percentiles compared with infants of married mothers. The result using birthweight continuously also shows that single mothers give birth to infants who are on average 99g lighter than do married mothers (Table 7.2). These odds ratios and the decrease in weight are slightly smaller than those using the NZCDS dataset (see Table 5.3).

The analysis of mothers in defacto relationships shows a non-significant risk of an infant below the 3rd percentile but a significantly increased risk of an infant between the 3rd and 10th percentiles. The decrease in birthweight when used as a continuous outcome is 88g which is similar to that for single mothers. However, the odds ratios suggest they are not as likely to have the very small infants. This is discrepant from the NZCDS dataset which at the univariate level suggested that mothers in defacto relationships were more like married mothers than single mothers (see Table 5.3).
7.2.4 Maternal and Paternal Education

The variables for maternal and paternal education are problematic due to the fact that there is a large amount of missing data, i.e. 40% for mothers and 47% for fathers. Therefore, the results may not be representative of the whole sample. Education is measured here by using the number of years of secondary school education. Both maternal and paternal education show similar patterns, with parents of less than 3 years of secondary education being more likely to have an infant below the 3rd percentile compared to those with tertiary education (Table 7.2).

When the group of infants between the 3rd and 10th percentiles are considered, the group shown to be at greatest risk is those with three years of secondary school education (i.e. to school certificate level). It may seem strange that this group is at higher risk than the group of lowest education, but this may be due to the fact that the lower educational group has been shown to have an increased risk of an infant below the 3rd percentile (Table 7.2).

For the continuous outcome both maternal and paternal education have little effect on birthweight. The only significant difference shown is a decrease in birthweight of 68g amongst infants of mothers with less than three years secondary education.

7.3 Maternal Smoking

Smoking is considered to be the most important factor in relation to birthweight. Information was available from this dataset on the number of cigarettes smoked per day both prior to and during pregnancy. Hence, analysis will be able to determine the importance of dose and timing of the insult to the fetus.

7.3.1 Smoking Prior to Pregnancy

The risk of an infant being below the 3rd percentile increased with the number of cigarettes smoked per day prior to pregnancy, in comparison with those that did not smoke. There was a slight non-significant increase in risk of being below the 3rd percentile for those for whom information was not available. Another point of interest was the unexpected trend in risks, with the group that smoked less than 5 cigarettes per day having a
similar point estimate to those who smoked 5-9 per day. Also, those smoking 10-19 per day had a similar point estimate to those who smoked 20 or more per day (Table 7.3). Using only observations for which smoking was known, a test for linear trend gave a $\chi^2$ of 20.915 compared to an overall $\chi^2$ of 26.14, the difference of 5.225 with 3 degrees of freedom ($p=0.1560$). This shows that the difference from the expected distribution is accounted for by a linear trend.

When between the 3rd and 10th percentile is considered as the outcome of interest, the pattern is more like that which one would expect. That is, there is an increasing risk with increasing number of cigarettes smoked per day. However, the risk for those that smoke 1-4 cigarettes per day is non significant. The group for whom information is unavailable shows no difference in risk. As with the test for linear trend for the below the 3rd percentile, the departure from the expected distribution was accounted for by a linear trend (overall $\chi^2=29.51$, trend $\chi^2=28.348$, difference=1.162 (d.f=3, $p=0.7621$)).

Using birthweight as a continuous outcome shows a similar decrease in weight for those smoking 1-4 and 5-9 cigarettes per day and also for those smoking between 10-19 and 20 or more cigarettes per day. The change in birthweight for the latter groups is almost double that of the lower smoking groups compared to non-smokers. This outcome also shows a significant decrease in birthweight for the unknown group, suggesting that this group includes some smokers (Table 7.3).

### 7.3.2 Smoking During Pregnancy

The first point of note with this variable is the decreased number of smokers in all smoking groups. The relationship between the number of cigarettes smoked during pregnancy and the risk of being below the 3rd percentile was similar to that of the relationship with cigarettes smoked prior to pregnancy, in that the risks were increased. The odds ratios among the smoking groups are generally higher than those for smoking prior to pregnancy. However, there seems to be no consistency in the pattern and the results are not as clear as those for smoking prior to pregnancy (Table 7.3). Unlike smoking prior to pregnancy, even though the overall $\chi^2=41.59$ and the trend $\chi^2=29.007$ are significant, the pattern of risk is not explained by a linear pattern (difference=12.528 ($p=0.0056$)).

Again, with the group of infants between the 3rd and 10th percentiles, the risks are at an increased level to those from smoking prior to pregnancy. The relationship here also shows a similar risk for those who smoked 1-4 cigarettes per day to those who smoked 5-9 cigarettes per day. The 10-19 cigarettes per day group also
has a similar risk, not as in the prior to pregnancy analysis where the risk was similar to that of the 20+ group. Looking at the continuous response shows a decreasing birthweight with increasing smoking category. Differences in the two lower and two higher categories were similar, as they were in the prior to pregnancy analysis. There was no significant decrease in birthweight for the group with missing data (Table 7.3). As in the analysis for below the 3rd percentile the pattern in the risk associated with smoking was not accounted for by a linear pattern (overall $\chi^2=48.13$, trend $\chi^2=38.744$, difference=9.386 ($p=0.0246$)).

This information allows for analysis of both smoking prior to and during pregnancy. To do this it will be appropriate to exclude from the analysis infants for which smoking information either prior to or during pregnancy was unknown.

### 7.4 Genetic Factors

#### 7.4.1 Ethnic Group

Ethnic groups show differences in the size of newborn infants. This may be due to maternal characteristics such as height and weight, or due to cultural practices. This dataset allowed more ethnic groups to be defined than in the NZCDS dataset, with Asian (mainly Chinese and Indian) ethnicity also able to be defined.

The only group to show an increased risk of being below the 3rd percentile were Asian infants who had an almost three fold increased risk in comparison to European infants (Table 7.4).

Considering those between the 3rd and 10th percentiles, Asians were at a two fold increased risk and Maori at a one and a half fold increased risk compared to Europeans. Pacific Island mothers on the other hand were at a reduced risk of having such an infant. There was also an increased risk for those in the "other" ethnic group. All these effects were significant at the 5% level (Table 7.4).

Using birthweight as a continuous outcome gives consistent results with Asians being 218g, and Maori being 97g, lighter on average than Europeans. The Pacific Island mothers had infants that were on average 141g heavier than Europeans while the "other" ethnic group also had lighter infants similar in weight to the Maori group (Table 7.4).
The risks and differences in weights for the infants of the Maori and Pacific Island women are of similar magnitude to those obtained at the univariate level in the analysis of the NZCDS dataset (Table 5.9).

7.4.2 Maternal Height

Maternal height was missing for over two thirds (67.1%) of women in the dataset, therefore the results should be interpreted with caution. Considering the \textit{a priori} categories (as were chosen for the NZCDS data), suggests an increased risk for shorter women and a decreased risk for taller women of having an infant below the 3rd percentile. Neither of these estimates however are significant at the 5% level. A test for linear trend, however, is significant $\chi^2=4.275$, and compared to an overall $\chi^2=4.36$ implies that the pattern of risk is linear.

The \textit{a priori} categories show an increased risk for women 160cm or shorter of having an infant between the 3rd and 10th percentiles, and a decreased risk for those 171cm or more. As with below the 3rd percentile the pattern of risk is accounted for by a linear pattern.

These categories also show an increased birthweight for infants of the taller women and a decreased birthweight for infants of the shorter women when birthweight is used as a continuous outcome. Both these effects are significant and of similar magnitude (Table 7.4).

Whilst the odds ratios are similar in size, the magnitude of these effects using birthweight continuously are notably larger than those seen in the NZCDS dataset. However, like those in the NZCDS dataset, the estimates for the “short” and “tall” women are similar.

The Q-Q plot (Fig 7.1) for maternal height is similar to the plot using the NZCDS dataset with the cutoff points for the shorter and taller women similar to those suggested in the analysis of the NZCDS dataset (see Table 5.10). The small differences in cutpoints are likely to be due to slight differences in the populations that would be expected by chance. These cutoff points have very little effect on the risks using either categorical outcome or using the continuous outcome, since few observations changed categories from the \textit{a priori} ones due to the small amounts of data available (Table 7.4). Likewise, the patterns in the odds ratios continue to be accounted for by a linear trend. Hence either the \textit{a priori} or Q-Q plot categories are probably appropriate to use in this dataset.
7.5 Obstetric Related Variables

7.5.1 Maternal Age

Using \textit{a priori} categories, maternal age showed little effect at the univariate level when infants below the 3rd percentile were considered, although point estimates did increase with decreasing age category. The overall $\chi^2$ was not significant. However, a test for linear trend was significant. Looking at infants between the 3rd and 10th percentiles showed an increased risk for younger mothers (both the overall $\chi^2$ and the test for linear trend being significant), and the pattern of risk being accounted for by this linear trend. Similarly, the continuous response also shows decreasing birthweight with decreasing maternal age category (Table 7.5a).

The Q-Q plot of this variable (Fig 7.2), suggests that the maternal age categories are different from those chosen \textit{a priori} (Table 7.5a), however, any increased in risk (like in the NZCDS) looks to be small. The Q-Q categories for maternal age again show no effect on the SGA risk below the 3rd percentile and neither the overall $\chi^2$ nor the test for linear trend were significant. As would be expected, the odds ratios for those between the 3rd and 10th percentiles using Q-Q categories are greater than those of the \textit{a priori} categories. As with the \textit{a priori} categories they show increasing risks with decreasing age category. Unlike below the 3rd percentile however, the overall $\chi^2$ and test for linear trend are significant and the pattern of risk accounted for by the linear trend. The continuous response using the Q-Q chosen categories also shows larger decreases in weight with decreasing age category (Table 7.5a).

Whilst, in the analysis of the NZCDS, the Q-Q plot did not show any reason not to use the \textit{a priori} categories (in fact showed no real pattern), there is some evidence here that the Q-Q plot categories better define similar groups of individuals. Hence the Q-Q categories will be used in further analyses.

7.5.2 Paternal Age

The variable for paternal age has missing values for 19.0\% of observations, therefore some caution should be used in interpreting the results.

\textit{A priori} categories for paternal age were the same as those for maternal age. Similarly, there were no increased risks for an infant below the 3rd percentile in any age grouping, nor were overall $\chi^2$ or a test for
linear trend significant. There were however, significantly increased risks of infants being between the 3rd and 10th percentiles when the father was between 20-24 or 25-29 years of age, compared with those 30 years or more of age. A test for linear trend proved to be significant and accounted for the pattern of risk. The continuous outcome suggested a relationship similar to that of maternal age, i.e. decreasing age associated with smaller infants (Table 7.5a). These effects are similar to those of maternal age, and may in part be because paternal and maternal age are correlated (r=0.71 p=0.001).

The Q-Q plot (Fig 7.3) suggests slightly different cutoffs for categories of paternal age. These categories are also different from those for maternal age. However, it should be remembered that there is missing data which may have an effect. When these cutoffs are used, there is again no increase in risk in any category for infants below the 3rd percentile and, as in the a priori situation, the overall \( \chi^2 \) and test for linear trend were not significant. The Q-Q categories though show increasing risk with decreasing age category when those between the 3rd and 10th percentile are considered, and the pattern of risk is of a linear nature. Likewise, the continuous outcome shows decreasing birthweight with decreasing age (Table 7.5a). Paternal age will be used in Q-Q categories in further analyses. Also of note are the very similar patterns and magnitudes of point estimates, especially using the continuous outcome, comparing the effects of maternal and paternal age.

### 7.5.3 Antenatal Admissions

Antenatal admissions to hospital were measured by both number of admissions and by the number of days mothers were admitted for. A single admission showed significantly increased risks of having an SGA infant, the risk being higher in the less than 3rd percentile category. The use of a continuous outcome shows a consistent result with a significant decrease in birthweight of 72g on average. Mothers with multiple admissions, however, show no difference in the risk of an SGA infant, (likewise the decrease in birthweight is not significant) (Table 7.5b).

When the number of days of admission is considered, those with 1, 2, or 3 or more days in the antenatal ward are at increased risks of an infant below the 3rd percentile, although the risk for those in for only 1 day is not significant. The risks of having an infant between the 3rd and 10th percentile are not significant. Using birthweight as a continuous variable does not show a significant decrease in weight for 1 day of admission but does show significantly decreased birthweight with 2 and 3 or more days of admission. The later categories will be combined (Table 7.5b). Due to the inconsistencies and no notable pattern, a variable for any antenatal admission will be used in further analyses.
7.5.4 Ultrasounds

The number of ultrasounds is missing for a large proportion of observations (67.4%), thus the results should be interpreted with extreme caution. The results suggest that 1 or 2 ultrasounds are associated with a similar SGA risk to each other, but that women with 3 or more ultrasounds are at increased risk of having an SGA infant. This result is consistent with that when a continuous outcome is used. Infants of mothers with 3 or more ultrasounds during pregnancy are approximately 100g lighter (Table 7.5b). Mothers who had no ultrasounds showed an increase in birthweight, however, this was not significant and the binary outcomes showed no consistent pattern.

7.5.5 Maternal Antenatal Visits

There are no a priori categories for the number of antenatal visits and hence a Q-Q plot was used. The Q-Q plot (Fig 7.4) showed little deviation from the line indicating unity, and the points showing the largest changes in gradient were chosen as cutoffs. There were no significant effects of the number of antenatal visits on any of the outcome variables (Table 7.5b).

7.5.6 Blood Pressure During Pregnancy

Maximum diastolic blood pressure was measured both before and after 20 weeks gestation. It was recorded in broad categories, as shown in Table 7.5c. Over a third of the observations had missing information for these variables. Nearly all women (97.5%) who had their blood pressure measured before 20 weeks gestation had a measurement <90mmHg. Blood pressure is known to increase after 20 weeks gestation and this was also noted here.

There were no significant increased SGA risks shown for any blood pressure group after 20 weeks gestation. However, the data did suggest an increasing risk with increasing blood pressure for the less than the 3rd percentile category. Between the 3rd and 10th percentiles, the blood pressure groups showed no significant differences. Using birthweight continuously showed no effect of increasing blood pressure on birthweight and no pattern was noticeable.
Simplifying the blood pressure variables to an increase in blood pressure category from the ‘before 20 weeks gestation’ measurement to ‘after 20 weeks gestation’ measurement showed a slightly increased odds ratio using the binary outcomes, that for the 3rd to 10th percentile outcome being significant at the 5% level. Using the continuous outcome showed no significant difference in birthweight with blood pressure (Table 7.5c).

7.5.7 Maternal Haemoglobin During Pregnancy

Haemoglobin (Hb) levels were missing for approximately half (54.2%) of the women in the dataset, hence the results should be interpreted with caution. There were no consistent a priori categories in the literature. Therefore a Q-Q plot (Fig 7.5) was used to determine appropriate cutoff points for categories along with previously used a priori categories. The cutoff points showed no trend when the various outcomes were used. The highest risk group when the outcome was below the 3rd percentile was Hb between 101 and 108. However, this was the group at lowest risk when between the 3rd and 10th percentile was used as the outcome. Using this outcome, a slight significant increase in risk was found for those with Hb between 109 and 124. Using birthweight as a continuous variable again showed no trend and no difference in birthweights between any of the categories (Table 7.5c).

7.5.8 Multiple Pregnancies

Both infants of a set of twins were at an increased risk of being below the 3rd percentile, the first born being at nearly five times increased risk and second born more than ten times increased risk of being a SGA infant. Using between the 3rd and 10th percentiles outcome the second born twins were again at an increased risk, although first born twins were at no greater risk of being SGA than singletons (Table 7.5c).

Using a continuous outcome, first born twins are on average 355g lighter than singletons while second born twins have yet a further decrease in birthweight, being 495g lighter on average. Hence first born twins are lighter than singletons and second born twins even lighter.
7.5.9 Previous Live Births (Parity)

The number of previous live births shows the expected relationship at the univariate level, i.e. subsequent pregnancies are at lower risk than the first of producing an infant either below the 3rd percentile or between the 3rd and 10th percentiles (Table 7.5d). The second and third pregnancies show a similar risk and it may be reasonable to combine these, as was the case in the NZCDS dataset (Table 5.17). Both categorical outcomes however, show a significant test for linear trend $\chi^2=16.791$ (p<0.0001), and $\chi^2=22.443$ (p<0.0001) respectively. Comparing these tests to the overall $\chi^2$ (20.92 and 27.64 respectively), showed that the linear pattern accounts for most of the difference in pattern from the expected distribution. Using the continuous outcome also shows increasing birthweight with increasing parity (again with the second and third pregnancies not dissimilar). This is somewhat contrary to the NZCDS dataset where there was little difference in birthweight beyond the first pregnancy (Table 5.17). Both the binary and continuous outcomes show further reduced risks (increases in birthweight) for mothers with three or more previous births. This, then, suggests a beneficial effect of grand multiparity on birthweight (Table 5.17). One possible reason for the differences in the results between these studies may be the small number of women in the NZCDS dataset who are grand multiparae.

7.5.10 Previous Miscarriages and Induced Abortions

Neither the previous number of miscarriages nor the previous number of induced abortions show any relationship to birthweight or the categorical outcomes. Since these two variables may be considered to be previous pregnancies, one might expect them to produce a protective effect, this does not, however, seem to be the case (Table 7.5d).

7.5.11 Previous Low Birthweight Infant

Women who had previously given birth to an infant less than 2500g were more likely to have an infant between the 3rd and 10th percentiles. This was consistent to that using the continuous outcome. Mothers who had previous low birthweight infants gave birth to infants 126g lighter on average than mothers without a previous infant less than 2500g. This effect may be even greater given the increase in weight previously mentioned for other than first infants (Table 7.5d). Hence there is a need to control for the number of previous live births when considering this variable.
7.5.12 Previous Caesarean Section

Women who had previously had a caesarean section were less likely to have an infant between the 3rd and 10th percentiles. This result was consistent with that using birthweight continuously. Women that had previously had a caesarean section giving birth to infants who were on average 99g heavier (Table 7.5d). This is likely to be confounded by the number of previous pregnancies, since first born infants are usually smaller than subsequent siblings.

7.5.13 Inter-birth Interval

Inter-birth interval may also play a part in the size of subsequent infants. This variable, naturally, can only take into account women who have had a previous pregnancy. The data gave only the year of the previous pregnancy and hence only an approximation was able to be made of the inter-birth interval. Due to the possible inaccuracies of the data a Q-Q plot was not considered. The impression from this data, however, is that periods up to five years between births does not seem to have any effect on the risk of an SGA infant or the infant’s birthweight. Women who have more than 5 years between pregnancies, though, seem to have an increased risk of having an infant below the 3rd percentiles and their babies are on average 61g smaller, both these effects being significant at the 5% level (Table 7.5d).

7.6 Nutrition and Work in Pregnancy

7.6.1 Maternal Work During Pregnancy

Maternal work in pregnancy is related to a number of variables including socio-economic status, parity, and nutrition. Full-time work during pregnancy showed little effect using the percentile cutoffs, though using a continuous outcome showed an average decrease in birthweight of 49g, significant at the 5% level (Table 7.6).

On the other hand, part-time work is seen to be a non-significant risk for those below the 3rd percentile, but was significantly protective for those between the 3rd and 10th percentiles. The continuous outcome showed little difference in birthweight in comparison to those who did not work during pregnancy.
These results are somewhat confusing and seemingly at odds with each other. This analysis was unable to take into consideration the timing and length of work during pregnancy. Furthermore, a reasonably large proportion of women (21.2%) have information missing for this variable which may also influence the results.

7.6.2 Maternal Weight Gain in Pregnancy

The a priori categories for maternal weight gain were obtained from previous work in the literature.\(^{240}\) Whilst not significant, there was a suggestion that those with lower weight gains per week during pregnancy were more likely to have infants below the 3rd percentile. Using between the 3rd and 10th percentiles as the outcome also showed increased risks for those in the lower weight gain categories, however, only the low-moderate weight gain category showed a significant effect at the 5% level (Table 7.6). The continuous outcome showed decreasing birthweights with decreasing category of maternal weight gain, all of these differences being statistically significant (Table 7.6).

The Q-Q plot (Fig 7.6) suggested different points for the cutoffs and these categories showed similarly sized risks for the two lowest weight gain categories, when below the 3rd percentile was used as the outcome, these risks were not quite statistically significant at the 5% level. Using the outcome variable for between the 3rd and 10th percentiles, the changed cutoffs showed increased risks for the three lowest weight gain categories, compared to the baseline category, although the highest risk remained in the middle one of these categories. The lowest weight gain category showed no significantly increased risk. Using the continuous response again showed decreased birthweights in these three categories and the pattern found was similar to that of the odds ratios, i.e. the greatest decrease in weight was amongst those in the low to moderate weight gain category (Table 7.6).

7.7 Distribution of Observations with Missing Variables

Variables where missing data was a problem were considered at the univariate level in a similar manner to that for the smoking variables. A dummy variable was set up to indicate missing data. Examination of these categories using all three outcomes; below the 3rd percentile, 3rd to 10th percentile, and using birthweight continuously, found no significant differences between the missing data group and the base category in most cases. This suggests that the infants of mothers who had missing data were spread
across all the categories for these variables in a similar manner to the mothers for which data was available.

This is encouraging in respect to the interpretation of results using only the observations for which data was available for all variables.
Chapter 8: Multivariate Analysis of National Women's Hospital Dataset

The previous chapter looked at the relationship between the outcomes of below the 3rd percentile for gestation, between the 3rd and 10th percentiles, and birthweight as a continuous variable with the independent variables. Some of these variables have large amounts of missing data, and hence are unable to be used in a multivariate analysis, due to the number of observations that would be lost. These variables are: maternal work, maternal and paternal education, paternal age, blood pressure, inter-birth interval, number of ultrasounds, haemoglobin, antenatal visits, maternal height and maternal weight gain in pregnancy.

There are, however, a number of potentially important variables which have information for most if not all observations allowing multivariate analysis to be carried out.

When more than two outcomes exist i.e. we have a polytomous situation instead of a binary situation, it may be appropriate to carry out a multilevel logistic regression. This is done in a similar manner to that of a logistic regression with the exception that two intercept terms are fitted. This method therefore makes the assumption that no matter how the definition of the categories is made, moving from one dichotomy to another has no effect on any coefficients in the model other than the intercept.

When this situation exists one can use the Score test for the proportional odds assumption to test whether this assumption holds. In the case of the models in chapter 8 the assumption did not hold and it was decided that it would be more appropriate to perform separate logistic regressions for (i) <3rd percentile v >10th percentile, and (ii) between 3rd and 10th percentile v >10th percentile.

For further confirmation of the reason for doing this a table (Table 8.6) has been included of the full model which shows the odds ratios that are produced as a result of performing a multilevel logistic regression.

Therefore multivariate models will be considered for each of the three outcomes (2 binary, and continuous) in turn. The variables for which there are large amounts of missing data will be considered further in an attempt to gauge any effect they may have. This will be done by using the full model, plus the addition of each variable individually for which missing data was a problem.

The first issue, however, relates to the effects of smoking, prior to, and during pregnancy. The relationship between these variables and the three outcome variables will be considered before fitting the full models.
Full and reduced models were fitted in the same way as in Chapter 6 using the NZCDS dataset. Firstly all variables were placed in the model (full model). The model was then reduced. Variables were removed from the model one by one to ensure they did not have any major effects on the estimates of other variables due to confounding. Some variables were retained in models, even though they did not show significance, due to the size of the point estimates.

8.1 Effects of Smoking Adjusting for Ethnicity

It is appropriate to adjust the effects of smoking for ethnicity since the percentiles are derived from the whole population and because maternal smoking is related to ethnicity. The make up of ethnic groups in New Zealand (and especially the Auckland population), is changing over time and this may affect percentile definitions. It may also be appropriate to adjust these odds ratios for gestational age since smoking is also known to affect gestation. However, for this analysis, only ethnicity will be controlled for when considering the binary outcomes, as the binary outcomes already effectively control for gestation.

Another way of looking at the effect of smoking is to use the number of cigarettes smoked as a continuous variable. A logistic regression enables calculation of an odds ratio which indicates ‘the risk per cigarette per day’, and using a continuous outcome is ‘the number of grams decrease in weight per cigarette per day’. Hence, the risk of smoking n cigarettes per day is $\text{OR}^n$ for a binary outcome, and $n$ times the decrease in weight for the continuous outcome. The main problem with this approach is that odds ratios are difficult to interpret in this format. Another point of subjectiveness is that when people report the number of cigarettes they smoke in a day it is often in increments of 5 cigarettes. This occurs in 52.2% of those who reported smoking prior to pregnancy and 49.5% of those who reported smoking during pregnancy. Hence, a regression, as above, does not necessarily show the appropriate relationship. This also assumes that the relationship between the number of cigarettes and the outcome of interest is a linear one.

Due to the proportion of observations for which the number of cigarettes smoked per day was a multiple of 5 and, given this, the difficulty in interpreting the results, the analysis using the number of cigarettes per day as a continuous variable was not carried out.
8.1.1 Smoking Prior to and During Pregnancy

Of interest are the joint effects of smoking prior to and during pregnancy and what effects, if any, there are from reducing or increasing the amount smoked during pregnancy, or of quitting smoking during pregnancy. Approximately 10% of women changed their smoking habits between prior to pregnancy and during pregnancy. In mothers of infants above the 10th percentile 4.1% reduced the amount they smoked and 5.8% quit altogether.

When time of smoking is considered, without any measure of the amount smoked, an interesting pattern emerges. Looking at the outcome of below the 3rd percentile shows an increased risk for infants of mothers who smoked only prior to pregnancy. The risk was higher for those whose mothers smoked in both periods but reduced the amount smoked during pregnancy and was higher again for those who did not change their smoking habits from before to during pregnancy. Of further interest is the higher point estimate for the group of mothers who smoked only during pregnancy. This risk was not, however, significant at the 5% level. This group of women is very small, hence, the confidence interval is large (Table 8.1).

When the outcome of interest is between the 3rd and 10th percentiles, the pattern is similar although those who smoked only prior to pregnancy are not at a significantly increased risk. The odds ratios among the other groups are also smaller than for below the 3rd percentile outcome, suggesting a trend across the percentiles.

Using the continuous outcome a similar pattern is seen. There is a significant decrease in birthweight for those who smoked prior to pregnancy only. The decrease in birthweight is double for those who continued to smoke but reduced the amount smoked during pregnancy. The decrease in birthweight is doubled again for those who did not change their smoking habits during pregnancy. The change in birthweight for those who smoked only during pregnancy has a large confidence interval, as in the binary situation, but the point estimate is similar to the decrease in birthweight for those who reduced the amount smoked during pregnancy (Table 8.1).

Looking at the size of the odds ratios and decreases in birthweight for smoking prior to pregnancy only and during pregnancy only, the effects seem to be larger for those who smoked during pregnancy than those who smoked prior to pregnancy (Table 8.1). It therefore seems that smoking during pregnancy may be more important where birthweight is concerned.
This also seems to be emphasised with the effects of reduction in the amount smoked during pregnancy and of quitting smoking during pregnancy. Those who reduced the amount smoked and those who quit smoking during pregnancy did not have as large a risk as those who continued to smoke during pregnancy (Table 8.1).

Smoking prior to pregnancy and during pregnancy are related to each other. Hence, the effects reported thus far for the two behaviours are not independent of each other and are unlikely to be additive. Putting the variables for smoking prior to and during pregnancy in a model together suggested amongst all three outcome variables that smoking during pregnancy was the more important of the two periods (Table 8.2). The effects are naturally reduced due to the close relationship of these two variables and the likelihood of multicollinearity in the model. Thus it is sensible that only the dose from one of the two periods should be placed in the multivariate analysis, when dose is being considered.

Due to the greater effect of smoking during pregnancy it would seem that this would be the one which is chosen. The problem with this, however, is that it would make it difficult to interpret a term in the model for women who reduced the amount smoked, or quit smoking during pregnancy. For these reasons it was decided to include in the model the amount smoked prior to pregnancy, along with dummy variables for reduction during pregnancy, quitting during pregnancy, and smoking only in pregnancy.

Using the outcome of below the 3rd percentile, the unusual pattern that was apparent earlier with the lightest smoking group having a seemingly higher risk than those who smoked 5-9 cigarettes per day continued. The risks for those smoking 10-19 cigarettes per day and 20+ cigarettes per day are now similar. There is a notable decrease in risk for those who either reduced or quit smoking during pregnancy. Although neither of these reaches statistical significance at the 5% level, the pattern is one that makes sense, with those who quit smoking showing a greater reduction in risk than those who only reduced the amount smoked (Table 8.2). A large risk is also shown for those who smoked only during pregnancy. However, this group still has a large confidence interval due to small numbers.

An example of the interpretation of the risks is as follows. A mother who smoked 5-9 cigarettes per day prior to pregnancy has an increased risk of 2.99 of having an SGA infant compared to a non-smoker. This risk applies if the mother continued to smoke 5-9 cigarettes per day during pregnancy. If, however, the mother reduced the amount smoked during pregnancy to 1-5 cigarettes per day her risk would be 2.99*0.63=1.88. Furthermore, if the mother had quit during pregnancy her risk of giving birth to an SGA infant would be 2.99*0.51=1.52. Those mothers that smoke solely during pregnancy have an increased risk of 5.92.
For those between the 3rd and 10th percentiles, the pattern is similar to the univariate analysis (see Chapter 7), with risk increasing with an increasing number of cigarettes smoked during pregnancy. The risk for quitting during pregnancy is statistically significant for this outcome and halves the risk for the amount smoked prior to pregnancy. Reducing the amount smoked during pregnancy also continues to indicate a reduction in risk, whilst smoking only during pregnancy is again suggestive of a high risk. The increased risks are evident in the same manner for the 3rd to 10th percentile outcome, as described above for below the 3rd percentile.

The continuous outcome also follows a similar pattern to the binary outcomes, with the groups of smokers of 1-4 cigarettes per day and 5-9 cigarettes per day having almost identical decreases in birthweight. Those who smoke 10-19 cigarettes per day and 20+ cigarettes per day also had similar decreases in birthweight associated with them. The effect of reducing the amount smoked during pregnancy is to reduce the decrease in birthweight, and quitting smoking reduces the decrease in birthweight even further (Table 8.2). Those that smoked only during pregnancy still have a large confidence interval but the point estimate again suggests a decrease in birthweight.

The changes in birthweight using the continuous outcome are exhibited in much the same way as those for the binary outcomes. Using the same situation as before, a mother who smoked 5-9 cigarettes per day prior to pregnancy and continues smoking 5-9 cigarettes per day throughout pregnancy, on average gives birth to an infant 187g lighter than a non-smoker. If the mother had decreased the amount smoked to 1-5 cigarettes per day during pregnancy the change in birthweight would be -187+105=-82g, i.e. 82g lighter on average than non-smokers. If this mother had quit smoking the change in birthweight would be -187+148=-39, i.e. an infant on average 39g lighter than that of a non-smoker. Those that smoked only during pregnancy gave birth to infants on average 108g lighter than non-smokers.

The final format discussed above (smoking prior to pregnancy, along with dummy variables for reduction of smoking, quitting smoking, and smoking only during pregnancy) will be that which will be used for estimating the risk due to smoking in the multivariate models discussed in the rest of this chapter.
8.2 Multivariate Model for Below the 3rd Percentile

8.2.1 Full Model and Model Reduction

The model was fitted with all variables from the univariate analysis for which missing data was not a problem. The model was then reduced by removing variables that had no significant direct effect on the outcome, or an indirect effect on the outcome \((p>0.05)\), and the effect was small. The effect was considered to be indirect if the removal of a variable did not have any significant effect of the size of effects of the other independent variables in the model (Tables 8.3a,b,c,d).

The variables were removed in the following order:

i) geographical area (Table 8.3a): Although a number of women from south Auckland and North Shore booked at National Womens Hospital may have higher risk pregnancies, these are more likely to be those that deliver preterm. There are no obvious reasons why geographical region should have any effect on birthweight after controlling for other social indicators.

ii) previous miscarriages (Table 8.3d): The number of previous miscarriages showed no relationship at the univariate level and this is unchanged in the multivariate situation. There is a possibility that miscarriages and parity may confound each other, this however does not seem to be the case in this dataset.

ii) previous induced abortions (Table 8.3d): The arguments for this variable are the same as those for previous miscarriages.

iv) Marital status (Table 8.3a): The variables denoting marital status were also non-significant. Marital status tends to be a marker of socio-economic status. Hence the removal of the variables for marital status were most likely to have had some effect on the size of the effects of smoking, since smoking is a close marker of socio-economic status in the model. There was little effect on the odds ratios associated with smoking when marital status was removed. Therefore the variables for marital status were not retained in the model.

v) Previous caesarean section (Table 8.3d): Like previous miscarriages and induced abortions, a previous caesarean section had no notable direct effect on the model or indirectly.
vi) Booking trimester (Table 8.3a): Booking trimester may be another social indicator. However, the point estimates were in a direction different from what would be expected if this were the case. It did not quite reach statistical significance at the 5% level.

vii) Ethnicity (Table 8.3b): The final adjustment to the model was to combine the Maori, Pacific Island and "other" ethnic groups with Europeans as they showed no difference after controlling for available confounders. Therefore, Asian mothers were compared to mothers from all other ethnicities.

Of the variables remaining in the model, none were of a socio-demographic nature.

As in Chapter 6, the full and reduced models had different numbers of observations so a Chi-Squared test was unable to be performed to test for the adequacy of the reduced model.

Looking at the factors which the birthweight percentiles are based on, i.e. gestation and sex, there was a suggestion of a slight increase in the risk of being below the 3rd percentile at 41 weeks gestation, but there was no significant difference in risk for gender. Although this is relatively reassuring, it may indicate that the 3rd percentile curve may be unstable, particularly at higher gestations (Table 8.3a).

The only maternal lifestyle variable in the model is smoking (Table 8.3b). The model clearly shows an increased risk amongst smokers of having a small infant. What remains unclear, however, is the pattern in regard to dose. This may be due to splitting so few smokers into this number of groups. There remains, however, a significant reduction in risk for those that quit smoking during pregnancy and a clear indication of a reduction of risk for those who reduced the amount smoked during pregnancy. There is also an indication of a much increased risk among those that only smoked during pregnancy, even though this group has very small numbers (Table 8.3b).

The only genetic factor for which there was enough information to be included in the multivariate analysis was ethnicity. The only effect with this outcome was a four and a half fold increased risk for Asian mothers in comparison to all other mothers (Table 8.3b). This relationship may be of great importance with a fast growing Asian population in Auckland at present.

Most of the obstetric related variables in the model showed patterns much as would be expected. There was a decreasing risk with an increasing number of previous pregnancies, all these categories showing significantly decreased risks. Mothers who had previously given birth to a LBW infant had more than a two
and half fold increased risk of having an infant below the 3rd percentile. Mothers who were admitted to the antenatal ward were at twice the risk of having an infant below the 3rd percentile. Multiple pregnancies as expected remained significantly associated, with first born twins being more than 7 times more likely to be below the 3rd percentile and second born twins more than 13 times as likely to be below the 3rd percentile (Table 8.3c,d).

The exception with respect to expected patterns was that of maternal age, using the 10th percentile Q-Q plot (since there were not enough observations to define Q-Q plots for below the 3rd percentile with any degree of stability). The defined categories of maternal age suggested a decreasing risk of a small baby amongst younger mothers (Table 8.3c). These effects did not however reach statistical significance, and may be tied up with the effects of parity.

### 8.2.2 Full Model with Additional Variables

In the case of the full model for below the 3rd percentile, those models using additional variables for which missing data was a problem, showed few significant effects (Table 8.3e,f). Those that did show an effect were:

i) Ultrasounds (Table 8.3f): Women who had 3 or more ultrasounds were at an increased risk, suggesting that these may be women who are seen to be at risk of a small infant or other pregnancy problems i.e. it may be a consequence of SGA rather than a cause.

ii) Maternal weight gain (Table 8.3f): The two lowest weight gain categories showed much increased risks over the baseline category, suggesting that women who have poor weight gain are more likely to have smaller infants. Those in the next to baseline category showed no difference in risk.

iii) Maternal height (Table 8.3e): The effects of maternal height were not significant, the direction of the point estimates were, however, in the expected direction. The shorter mothers being at increased risk and the taller mothers being at decreased risk of an infant below the 3rd percentile.
8.3 Multivariate Model for the 3rd Percentile to Below the 10th Percentile

8.3.1 Full Model and Model Reduction

The model for this outcome was fitted in the same manner as that for the infants below the 3rd percentile (Table 8.4a,b,c,d). The order of removal of the variables was similar to that in the model for below the 3rd percentile which is as follows: i) geographical area (Table 8.4a), ii) booking trimester (Table 8.4a), iii) number of previous induced abortions (Table 8.4d), iv) previous miscarriages (Table 8.4d). The arguments surrounding these variables are the same as in the case of the model for below the 3rd percentile (see Chapter 8.2.1).

v) Admission to the antenatal ward (Table 8.4c): Whilst showing an effect in the model for below the 3rd percentile, there were no obvious effects for this variable at either the univariate or multivariate level with this outcome.

vi) Marital status (Table 8.4a), and vii) previous caesarean section (Table 8.4d). The comments for these variables are as they were for the model for below the 3rd percentile (see Chapter 8.2.1).

viii) Ethnicity (Table 8.4b): In this model, the Maori and Pacific Island groups were again combined with the European group as they showed no differences after controlling for the available confounders. The “other” group was not combined as it continued to show significant differences to the comparison group. Hence this model has three ethnic categories i) Maori, Pacific Island and European, ii) Asian, and iii) “other”.

Hence, the model for between the 3rd and 10th percentiles is the same as for below the 3rd percentile with the additional removal of the variable for admission to the antenatal ward and the slightly different re-categorisation of ethnicity in the model.

Again, the full and reduced models had different numbers of observations so a Chi-Squared test was unable to be performed to test for the adequacy of the reduced model.

The variables on which the percentiles are based show no increased risk at any gestational age, or any increased risk for either of the sexes (Table 8.4a). This suggests stability of the defined birthweight percentiles for this population of infants, as defined in Chapter 2.
As in the model for below the 3rd percentile, there were no relationships with any socio-demographic variables (i.e. booking trimester, geographical area, and marital status) after reducing the model.

Again, the most important factor appears to be that of smoking. With this outcome there is a much clearer pattern than with the model for below the 3rd percentile. There is a significantly increased risk among all the smoking groups and the risk increases with the amount smoked. There is a significant reduction in risk for those that gave up smoking during pregnancy, and a clear indication of a reduced risk for those who decreased the amount smoked during pregnancy. Those who smoked only during pregnancy again seem to be at an increased risk, as would be expected, even though the confidence interval remains large (Table 8.4b).

As in the model for below the 3rd percentile, there is little in the way of a relationship of ethnicity with this outcome (Table 8.4b). This is in contrast to the analysis of the NZCDS data where Maori mothers were shown to be at risk of an infant below the 10th percentile, and Pacific Island mothers at reduced risk in comparison to Europeans and "others" (Table 6.20). This is unlikely to be due to the removal of Asians from this group as this would be expected to increase the difference between European and Maori infants. Furthermore, the difference between European and Pacific Island would be expected to remain different due to the magnitude of the difference previously shown. This model shows that Asian mothers are more likely to have infants between the 3rd and 10th percentiles as well as below the 3rd percentile (see Table8.3b) compared to the combined ethnicity group. The group classified as "other" also continue to show an increased risk with this outcome. The ethnic make-up of this "other" group is unknown.

The obstetric related variables show similar effects to those of the model for below the 3rd percentile (Table 8.4c,d). There is a decreased risk with increasing number of previous pregnancies. However, in this model, this seems to be countered by the effect of maternal age which will be described shortly. As in the NZCDS dataset, the decreased risk is similar for those who have had either 1 or 2 previous pregnancies (Table 5.17). Those mothers that have previously given birth to a LBW infant were also at an increased risk of having an infant between the 3rd and 10th percentiles. The relationship of multiple pregnancies is not as notable here, with first born twins not being at a significantly increased risk. Second born twins, however, continued to be at an increased risk being four and half times more likely to be between the 3rd and 10th percentiles than singletons. Hence the suggestion is that twins are more likely to be below the 3rd percentile.

In contrast to what one would expect were the effects due to maternal age. There was an increasing risk with decreasing age of having an infant in this outcome group, however, the effect was only significant for the
youngest group of mothers (Table 8.4c). This is in the opposite direction to that for maternal age using the outcome of less than the 3rd percentile. This effect seems to counter to some extent the effect of parity as previously mentioned.

8.3.2 Full Model with Additional Variables

The additional variables which were included in the full model can be seen in Tables 8.4e and 8.4f. The only variables where an effect was seen were; maternal height, fathers age, blood pressure increase and maternal weight gain in pregnancy. No other variables showed any additional effect. These variables will be discussed briefly:

i) Maternal height (Table 8.4e): The model showed an increased risk for shorter mothers which was not quite significant at the 5% level. Also shown, however, was a significantly decreased risk for “taller” mothers. It had been thought that the effect of maternal height may remove the significant effect of being of Asian ethnic origin. This, however, was not the case.

ii) Paternal age (Table 8.4e): The variable for father’s age showed a decreasing risk with increasing age, the only significant effect, however, was an increased risk for the youngest fathers.

iii) Blood pressure increase (Table 8.4f): An increase in blood pressure categories from before 20 weeks gestation to after 20 weeks gestation was associated with a slight risk.

iv) Maternal weight gain (Table 8.4f): Whilst the increased risk for those in the lowest weight gain category was not significant, that in the next two lowest weight gain categories was significant. Suggesting that mothers with low weight gain have increased risks of SGA infants. The non-significant risk for the lowest weight gain category may be due to the increased risk of this group to have an infant below the 3rd percentile.
8.4 Multivariate Model Using Birthweight Continuously

8.4.1 Full Model and Model Reduction

As in the cases described above with a binary outcome, the model with a continuous outcome was fitted by placing all variables in the model and removing those that were not significantly associated with the outcome and did not affect the relationships between the other independent variables and the outcome (Table 8.5a,b,c,d).

Carrying out this procedure, the variables were removed from the model in the following order: i) geographical area (Table 8.5a), ii) number of induced abortions (Table 8.5d), iii) previous miscarriages (Table 8.5d). (The categories for no, one and two, previous miscarriages were combined as they showed no differences in birthweight, the dummy variable for three or more previous miscarriages however continued to show significance.) iv) admitted to the antenatal ward (Table 8.5c).

This is notably the same order that the variables were removed from the model with the outcome for between the 3rd and 10th percentile model, with the exception that booking trimester has not been removed from the model.

As was the case in Chapter 6, testing whether the subset of parameters fitted the model equally well has the same problem as in the binary models above, in that the full and reduced models have different numbers of observations.

The percentile specific variables produced results as expected. Gestational age showed large differences in birthweight, with an increase in birthweight with increasing gestation, which remain relatively unchanged from the univariate associations (Table 8.5a). There was also a notable difference in size between male and female infants, which is also unchanged from the univariate level. Hence confirming the need for sex specific birthweight percentiles if one is going to classify infants as SGA.

The socio-demographic variables differed in the pattern they had shown using categorical outcomes. Unlike in the models with a binary outcome, there were significant associations between marital status and birthweight. Marital status showed similar sized decreases in birthweight of infants born to single mothers and mothers in defacto relationships, compared to those who were married. However the decreases were not
large in size. Marital status is likely to be an indicator of socio-economic status, hence marital status itself is not the risk. Mothers who booked in the 2nd and 3rd trimesters of pregnancy also had slightly larger infants as suggested by the below the 3rd percentile model. This effect remains unexplained.

Smoking again showed a clear relationship with decreasing birthweight, there being significant decreases among all smoking categories (Table 8.5b). Still present are the similar decreases in birthweight for the 1-4 cigarettes per day and 5-9 cigarettes per day smoking groups and also the similar decrease in birthweight for the 10-19 cigarettes per day and 20+ cigarettes per day smoking groups. This suggests two groups of smokers; lighter smokers and heavy smokers. Also significant are the effects of either quitting or reducing the amount smoked during pregnancy. The model suggests that those mothers who smoked 1-4 cigarettes per day or 5-9 cigarettes per day prior to pregnancy, but then quit during pregnancy, have infants the same size as non-smoking mothers, perhaps suggesting the insult due to smoking occurs primarily during pregnancy. In addition, these lighter smokers are the ones that are also more likely to be able to give up smoking during pregnancy. This is supported by the point estimate of the decrease in birthweight amongst infants of mothers who smoked only during pregnancy. The confidence interval around this estimate remains large due to the small numbers of observations.

The relation of ethnicity to birthweight again showed very similar weights amongst European and Maori infants. This may be due to the effect of having controlled for smoking. The Pacific Island infants are notably larger, in contrast to the results seen using the binary outcomes. This could be due to the lack of control for maternal weight and height. Asian infants showed the same relationship as in the binary outcome case, being much smaller than Europeans. The group of “others” also had decreased birthweights (Table 8.5b).

The same patterns were seen for the obstetric variables using birthweight as a continuous outcome as were seen for the binary outcome (Table 8.5c,d). Increases were seen in birthweight with the increasing number of previous pregnancies, which seem to be relatively linear. There was a large decrease in birthweight amongst mothers that had previously given birth to a LBW infant. Twins, as would be expected, were of significantly lower weight, second twins being notably lighter than first twins. Also of note was an association between mothers with 3 or more previous miscarriages and birthweight. Although not quite significant at the 5% level, the decrease in weight was of notable size and hence this variable was retained in the model (the comparison group being those mothers with 0, 1, or 2 previous miscarriages). Maternal age showed slight decreases in weight for the younger mothers (less than 30). This was significant for those 23-29, but not those <23, this variable is likely to indicate socio-economic status to some extent.
8.4.2 Full Model With Additional Variables

The effects from variables with missing data, using the continuous outcome, were reasonably consistent with those for the binary outcome between the 3rd and 10th percentiles and are shown in Tables 8.5e, and 8.5f. The variables that showed significant effects are:

i) Maternal height (Table 8.5e): The effects for being shorter and taller were both significant using this outcome, and are of relatively large magnitude. The effect due to being taller was again notably larger than that of being shorter. Of note was the effect of ethnic origin, which remained significant.

ii) Fathers age (Table 8.5e): Using the continuous outcome showed similar decreases in birthweight point estimates for all the categories below 37 years of age. However only the groups for 25-30, and 31-36 showed a significant effect.

iii) Weight gain in pregnancy (Table 8.5f): Low weight gain in pregnancy was again associated with decreased birthweight. Using this outcome, however, all three lower weight gain categories showed significant effects. The two lower weight gain categories show similar decreases in weight and of double the magnitude of the other category. All these decreases in birthweight were substantial.

8.5 Comparison of Odds Ratios and Changes in Birthweight

Figure 8.1 is a plot (like that in Chapter 6) of the odds ratio versus the change in birthweight for each of the variables in the full model. The odds ratios used are those from the model using the outcome as between the 3rd and 10th percentiles.

As in the plot in Chapter 6 (Fig 6.1), the relationship between the two seems to be relatively linear. One point seems to be a little away from where the line of best fit, this point relating to a first born twin (Fig 8.1). As was noted in the analysis, these infants seemed only to be at increased risk of being below the 3rd percentile. Fitting a linear regression to the data produces a model with the relationship Change in birthweight=151.95-139.28*odds ratio. This suggests a larger decrease in weight per unit of the odds ratio than in chapter 6, although the intercept is slightly higher. This difference will in part be random and may also to be due to the limited number of variables that were able to be controlled for in this model.
8.6 Summary of the Multivariate Models

The model using a binary outcome as below the 3rd percentile for weight seems a little unstable. Most of the variables show the expected relationship with birthweight. However, some show no relationship when one is expected (i.e. socio-demographic variables), and one shows a relationship opposite to what might be expected (i.e. maternal age). It was expected that with a dataset of this size, and, hence, reasonable numbers below the 3rd percentile, that the model would be stable. This does not seem to be the case, perhaps because the numbers are still too small or because this group of individuals is not homogeneous.

Using the binary outcome that indicated infants between the 3rd and 10th percentiles, the relationship of the independent variables were much as would be expected. The relationships would not be expected to be precisely the same as they were with the NZCDS dataset, as the group here excluded infants below the 3rd percentile. The model using birthweight continuously also, in general, showed relationships that would be expected and that made biological sense.

Summarising, the effects of gestation and sex show the need for sex specific percentile curves.

The socio-demographic variables showed no effect of geographical area. Such an effect would likely be due to socio-economic and ethnic factors, both of which are controlled for directly or indirectly in these models. Marital status is an indicator of socio-economic status and is related to many variables. The effect using birthweight continuously is small and, hence, probably explains the non-significance using a binary response. The effect of booking trimester using the model for below the 3rd percentile outcome, and again using birthweight continuously is unexplained.

The obstetric variables are generally consistent with expected results and show similar and biologically plausible results using all the outcomes. There is a decreased risk of having a small infant in subsequent pregnancies, and an increased risk amongst mothers who have previously given birth to a LBW infant. Twins, as would be expected, are also smaller, though this is not significant for first born twins using the 3rd to 10th percentile outcome. The only other obstetric related variable is that of admission to the antenatal ward which is only related to the outcome of below the 3rd percentile. This may indicate early recognition of some mothers likely to give birth to small infants. Younger maternal age seems to decrease birthweight slightly. This may be due to biological maturity but is not consistent in these models and seems to be inter-related with parity.
The effects of ethnicity are much as expected using the continuous outcome, though the relationships are not as clear using the binary outcomes. Smoking shows clear and substantial risks using all outcomes, and dose effects are detectable using the 3rd to 10th percentile cutoff. These patterns, seen in the 3rd to 10th percentile group and using the continuous outcome, are not however entirely consistent with each other. The 3rd to 10th percentile outcome shows an increase in risk with increasing amount smoked while the continuous outcome suggests the risks for 1-4 and 5-9 cigarettes per day are similar, as are the risks of 10-19 and 20+ cigarettes per day. There is a consistent trend for a smaller infant among those that smoke during pregnancy only. There is also a clear effect seen with all outcomes of the beneficial effects of reducing the amount smoked and even more so of quitting smoking during pregnancy.
Chapter 9: Relationships of Birthweight to Outcome Measures

Recent work has been reported by Barker et al. from England on the relationships of factors in early life and risk of disease in adult life. This work has been discussed more extensively in Chapter 1. One such report suggests that increased blood pressure in adult life is predicted by an increased placental weight to birthweight ratio. The AMSIS dataset that has been investigated for risk factors associated with SGA in the two previous chapters also contains data on other birth measurements, namely; placental weight, head circumference, and crown-heel length.

The ratio of birthweight to placental weight gives a simple measurement of how many times larger the infant’s weight is than the placenta. Similarly the inverse of this ratio is the proportion of the infant’s weight to placental weight.

9.1 Birthweight and Other Birth Measurements

A plot of birthweight against placental weight shows the relationship between the two variables. The plot showed two relatively distinct groups of points; a large group that one assumes are “normal” and a group who seem to have large placentae for their birthweight (Fig 9.1). A histogram of the ratio of birthweight to placental weight shows that this is indeed true (Fig 9.2). The histogram shows a second group with a ratio of less than approximately 3.5 (or a placenta more than 2/7's of the birthweight).

Due to the more limited ranges of head circumference and crown-heel length, this group of infants could not be distinguished on a plot using these variables against placental weight. However when this group was arbitrarily chosen as those with a birthweight:placental weight ratio of 3.5 or more (as shown in Fig 9.3), the plots of placental weight against crown-heel length (Fig 9.4) and head circumference (Fig 9.5) showed that these individuals were still a quite distinct group, not however, to the same extent as in the plot against birthweight. Therefore these individuals seem to have large placental weights in relation to all other birthweight measurements.

An important question therefore is "Who are these individuals and how can they be identified in relation to other factors?"
9.2 Definitions of Groups

The ratio between the weight of the placenta and birthweight can be used in one of two different ways. It can be used as a continuous variable or as a categorical variable, using defined cutoffs to determine which observations will fall into which categories.

In the case of a continuous response (the proportion of the birthweight to placental weight) there is an assumption that change in the size of the ratio from 0.2 to 0.25 is equivalent to a change of the ratio from 0.25 to 0.3. This may or may not be true and would need to be determined during the analysis of interest.

Using a categorical variable means splitting the observations into some number of groups. This could be done by fitting one or more discriminant functions to the data in order to separate the groups that are specified. Unfortunately, in this situation the groups are not pre-specified and for that matter it is not known how many groups exist. Of interest is the group of infants that have large placentae in relation to their birthweights, without knowing how this group should be defined.

9.2.1 Clustering Analysis: Euclidean Distances

Due to the difficulty of determining which observations should fall into which group, clustering analysis will be used to help determine how many groups there should be and hence which observations belong in which group.

Clustering analysis was performed using a two step method. The first step in the process is to standardise the data, this was done using Proc Standard in SAS. This procedure standardises variables so that they have a mean of nought and a standard deviation of one. The second step in the process is to use Proc Fastclus from SAS. This procedure uses the standardised variables to produce disjoint clusters based on Euclidean distances computed from the standardised variables. An example of the code used in standardising and producing clusters is provided in Appendix D.

The Fastclus procedure uses a method called "nearest centroid sorting". A set of cluster seeds is selected by the procedure and each observation is assigned to the nearest seed to form the required number of clusters. The seeds are then replaced by the means of the clusters and the process is repeated until no further changes occur in the clusters.
Euclidean distances are calculated by the simple distance between two points, so the Euclidean distance ($d_e$) from a point $(x_1, y_1)$ to a point $(x_2, y_2)$ is simply:

$$d_e = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

A cluster analysis based on Euclidean distances, using only birthweight and placental weight, was carried out since this seemed to be the most important relationship. Limiting the analysis to two clusters produced the result in Fig 9.6. The plot was not consistent with the group considered to be of interest. The groupings seemingly falling into high placental weight and birthweight and low placental weight and birthweight with more of an emphasis on placental weight.

Allowing three clusters in the analysis gave a result which was more consistent with that expected (Fig 9.7). The main body of data was split in two groups of similar size; one having lower birth and placental weights, the other having higher birth and placental weights. The third cluster produced was relatively consistent with the group of interest, however, this third cluster also contains a wedge of the main body of data. Additional clusters did not seem to add anything, and were basically sub-clusters of the clusters produced when three clusters were used in the analysis.

Since using placental weight and birthweight did not produce groups consistent with what was considered to be of interest all birth measurements (birthweight, placental weight, crown-heel length, and head circumference) were used in the cluster analysis using Euclidean distances (Figs 9.8, 9.9).

Using two clusters produced a large cluster containing most points, including those of interest, and a smaller cluster which merged into the large cluster when viewed on a plot of birthweight against placental weight (Fig 9.8). Allowing three clusters produced two clusters along similar lines to that of the two cluster analysis using only birthweight and placental weight, although, as in the two cluster analysis, the clusters merged into each other on the axes used and did not distinguish the points of interest. The third cluster was only small and of no note (Fig 9.9).

Again, the addition of more clusters did not help since the additional clusters were generally sub-clusters of those obtained allowing three clusters.
Another variable of importance in relation to birth measurements is gestational age. Using it along with the other birth measurements produced similar clusters in position and size to those previously described using the four birth measurements.

The possible problems in trying to cluster by this method is that the Euclidean distances do not take any account of the correlation between the variables. In the case of birthweight and placental weight there is a correlation of 0.50207 (p=0.0000). A method to take account of this correlation is called the Mahalanobis distance.

9.2.2 Clustering Analysis: Mahalanobis Distances

To take the correlation between the two weights into account one needs to use the Mahalanobis distances. These distances allow elliptically shaped clusters to be seen, as well as those of a more circular nature that would be picked up by the Euclidean distances. To carry out this analysis, the data was transformed using a Mahalanobis transformation. This transformation involves taking the inverse of the variance-covariance matrix, then computing a Cholesky decomposition on this matrix and pre-multiplying the data matrix by the lower triangular matrix of the decomposition. This transformation creates variables which have variances of 1 and co-variances of 0, and hence are not correlated. This transformed data was then re-analysed in the same manner as the untransformed data using Euclidean distances. The analysis was carried out in the same manner and using the same procedure as described in the previous section.

The analysis using just birthweight and placental weight and allowing two clusters produced the result which is shown in Fig 9.10. This figure shows clusters much more consistent with what were considered to be the groupings of interest. The split which defines the two groups seems to be of a linear nature. The group containing those individuals considered to have a large placenta also contains observations on the fringe of the upper side of the main body of data.

Allowing three clusters produces a similar cluster containing those of particular interest, though fewer are contained in this cluster from the fringe of the main body of data. The main body of data is then separated into two clusters split at approximately 3750g birthweight (fig 9.11). The group of interest using only two clusters is hence probably preferable since it contains a larger number of points and is likely to be more conservative.
Using all the birth measurements with or without gestation, and carrying out a Mahalanobis transformation, produced similar results. Allowing only two clusters produced a cluster with 16 (without gestation) and 17 (with gestation) observations gestation respectively, the cluster not been distinct from the main body of data. Allowing three clusters produced a cluster which again contained only a few observations, furthermore none of the clusters were distinct on the axes used (as had been the case using Euclidean distances and all birth measurements). These plots are not included as they contain no additional or important information.

So using a Mahalanobis transformation with birthweight and placental weight and carrying out a cluster analysis seems to best distinguish the group of interest, with two or three clusters seemingly producing the best results.

9.2.3 Clustering Analysis: Principal Components

Another method of allowing for the correlation between variables is to use a principal components analysis. This however produces identical results to the Mahalanobis transformation when only birthweight and placental weight are used and similar results when all birth measurements are used.

9.2.4 Modelling of the data

A problem in using cluster analysis is the desire to lead the clustering procedure in the right direction. This tendency would unfairly bias the analysis. Another problem is that, having defined clusters, it is difficult to define a function to categorise other observations. In order to overcome this problem, it was decided to fit a model to estimate placental weight. This would then allow identification of observations where placental weight was not well predicted by the other birth measurements.

The variables used in fitting a model to placental weight were those considered previously; birthweight, head circumference, crown-heel length, and gestation. Fetal weight grows in a cubic manner as demonstrated by the fitting of the percentile charts (Chapter 2), (even though quartic terms were included in the models the curves are generally S shaped). Whereas fetal weight increases slowly during early pregnancy and accelerates during mid to late pregnancy, placental weight increases rapidly in early pregnancy and decelerates at the time the fetus is growing.68,163
Fitting models to placental weight with these explanatory variables, and using terms up to and including the 3rd power, showed that crown-heel length was not predictive of placental weight when birthweight, head circumference, and gestation were included in the model. This may in part be due to greater inaccuracies that are likely when crown-heel length is measured. The fitted model was:

\[
95672 - 0.669913 \times \text{birthweight} + 0.000201 \times \text{birthweight}^2 - 1.543949 \times 10^{-8} \times \text{birthweight}^3 + 32.1254965 \times \text{head-circumference} - 0.006494 \times \text{head-circumference}^3 - 7026.481736 \times \text{gestation} + 172.774725 \times \text{gestation}^2 - 1.416980 \times \text{gestation}^3
\]

A cluster analysis was performed on the residuals to determine whether, having modelled the data, the pattern that had been detected previously was still present. The cluster analysis on the residuals produced a cluster similar to those using Mahalanobis distances, though the delineation between the clusters was not as clear (Fig 9.12). Allowing 3 clusters again produced a cluster containing the points of interest though, as when Mahalanobis distances were used, this cluster was less conservative than with 2 clusters. The third cluster produced included observations where the placenta seemed small in relation to birthweight (Fig 9.13).

A histogram of the residuals showed a bimodal distribution as seen with the birthweight:placental weight ratio as seen in Fig 9.2.

Residual values were calculated from this model and standardised so that they had a mean of 0 and a standard deviation of 1. As has been noted, the placental weights are in fact bimodal. However, for the purpose of defining the individuals in the second peak the residuals will be assumed to be normally distributed. Hence, observations with a standard deviation score of 2.245 or more should lie in the top 1.25% of residuals and those with a standard deviation score of 1.96 or more in the top 2.5% of residuals.

Having used a very crude cutoff of a birthweight 3.5 or more times the placental weight gave an indication of the number of observations that seemed to have large placentae in relation to other birth measurements. Using standard deviation score cutoffs of 2.245 and 1.96 respectively produced groups of 171 above a s.d. score of 2.245 and 47 between a s.d. score of 1.96 and 2.245. Similarly individuals with standard deviation scores of less than -2.245 and between a s.d. score of -2.245 and -1.96 were identified and included 14 and 28 observations respectively, demonstrating the non-normal behaviour of the residuals.
The group with a s.d. score of 1.96 or more was chosen as this would be expected to provide a conservative estimate of the group. Similarly those with a s.d. of -1.96 and below were excluded from the comparison group.

A plot of these identified observations mapped against birthweight and placental weight identified the observations of interest (Fig 9.14). The characteristics of these three groups in Table 9.1 shows that the infants identified in the below 2 standard deviation score group had slightly larger birthweights than the "normal" group with small placentae and were slightly longer. The infants of most interest with a standard deviation score of 2 or more were smaller with large placentae, slightly shorter and had slightly smaller head circumferences.

9.3 Who Are These Infants?

The AMSIS database provides a large number of variables grouped into the following categories; socio-demographic factors, obstetric history, antenatal information and infant information, as have been described in Chapter 7. This data allows investigation into whether or not these infants are identifiable and the reasons and/or risks of having a large placenta in relation to birthweight.

Univariate analysis showed some relationships of interest, although one related variable stood out. Of the multiple births, only 6 of 113 twins for which all birth measurements were available were not in the group of observations identified by the model. This produces almost a 1000 fold increased risk of twins being in this group. A regression using the birthweight/placental weight ratio instead showed a decrease in the ratio of 2.85 (Table 9.2).

What has been identified is the procedure used at National Womens Hospital when twins are delivered. Twins are often born with fused placenta: this placenta is not split for the purpose of weighing as it is often not obvious what proportion of the placenta belongs to which twin. Hence, the whole placenta is weighed and this total weight recorded for both twins.
9.4 Remodelling of Placental Weight

It becomes appropriate therefore that twins should be removed from this dataset for any further analysis between birth measurements. Removal of these data points produces what seems to be a more normal distribution of both birthweights and placental weights (Fig 9.15).

Since the method of modelling placental weight has been decided upon as the most appropriate method of defining groups of individuals of interest, this procedure was carried out again using this reduced dataset. The model fitted is similar to that previously used:

\[ 1328.604954 + 0.000039236 \times \text{birthweight}^2 - 2.49931 \times 10^{-5} \times \text{birthweight}^3 + 18.895209 \times \text{head-circumference} - 0.003756 \times \text{head-circumference}^3 - 54.085504 \times \text{gestation} + 0.009755 \times \text{gestation}^3 \]

Using the residuals in the same manner as before produces groups as seen in Fig 9.16. There are 230 observations in the group with larger placentae for birthweight, and 91 in the group with smaller placentae for birthweight. The characteristics for these groups can be seen in Table 9.3, which shows a number of differences to Table 9.1. The group below 2 standard deviation scores is now of similar birthweight with small placentae and slightly longer than the "normal" group. The more noticeable change, however, is in the group above 2 standard deviations. These babies have heavier birthweights than the "normal" group with larger placentae and only slight differences in crown-heel length and head circumference. In general these babies seem to be large babies.

9.5 Summary

In summary the analysis in this chapter has explored what seemed to be a distinctive group of individuals. This analysis identified that the basis of this group was twin pregnancies. This distinctive group is noticeable due to an artefact in the data. The plot of data with twins removed shows that both birthweight and placental weight among singletons seem to be relatively normally distributed. Hence a need to re-consider whether or not a group of infants exist with birth measurements that distinguish them from the majority of the population. This will be discussed further in Chapter 10.
Chapter 10: Relationships of Independent Variables to Outcomes Related to Placental Size.

10.1 Introduction

This chapter will consider two issues. The first is whether there is a distinctive group of individuals that should be defined using a binary outcome, or whether the ratio of birthweight to placental weight should be considered as a continuum. The second issue is how the ratio of birthweight to placental weight changes in relation to birthweight and placental weight individually.

10.2 Relationships Using Binary and Continuous Outcomes

Univariate analysis was carried out comparing the group with larger placentae (as defined by the model and shown in Fig 9.16) to the group considered to be normal, and also using a continuous ratio of birthweight to placental weight, using all observations.

Results obtained using a binary outcome and a continuous outcome are not always consistent, in that, while one outcome may show a relationship between the independent variable and the group with large placentae, the other outcome shows no relationship or a relationship in the opposite direction. Some examples are shown in Table 10.1.

In the case of gestation, the lower gestational ages suggest a decreasing risk of an infant in the large placentae group, whilst the continuous outcome suggests that the ratio of birthweight to placental weight is decreased (Table 10.1). Since birthweight increases with increasing gestation (Table 7.1), this implies that placental weight is not increasing at the same rate as birthweight around term. This is, however, in conflict with the result suggested by the binary outcome, which shows a decreasing risk with decreasing gestation. Given that it is known that placental weight is not increasing as much as birthweight at this time the result with the binary outcome has no basis.

Both maternal smoking prior to pregnancy and maternal smoking during pregnancy suggest decreasing ratios with increasing amounts smoked (Table 10.1). Birthweight decreases with increasing amount of maternal smoking. This suggests that smoking affects fetal weight at a greater rate than placental weight. Using the
binary outcome shows no increased risks amongst any of the smoking groups which implies no relationship to smoking. Hence, inconsistency between the two outcomes.

Similarly a decrease is seen in the ratio with decreasing maternal age (Table 10.1). Consistent with this was an increased risk of being in this group using the binary outcome. However this was only significant for the youngest group of mothers.

**10.3 Summary of Binary and Continuous Outcome Analyses**

There are some notable differences in the results produced using the binary and continuous outcomes. These differences between the binary and continuous outcomes are likely in part to be due to small numbers within categories. It seems from the evidence in Chapter 9 and here that both birthweight and placental weight should be considered as continuous outcomes.

Another possibility for the differences is that the analyses were slightly different in that whilst the analysis for the continuous outcome contained all 6323 observations, the analysis with the binary outcome contained all but the 91 observations contained in the group defined as having a small placenta for birthweight. It seems unlikely that this small number of observations would account for the differences between the two analyses.

**10.4 Relationship with Birthweight, Placental Weight, and Their Ratio**

As has been noted in the previous section, the ratio is affected by both birthweight and placental weight, and a change in either will alter the ratio. The relationships between the independent variables and birthweight (considered previously in Chapter 8) may differ slightly in this section compared to that reported previously. This is due to the requirement that all observations must have all birth recordings to be included in this analysis. These changes in birthweight will be considered alongside the relationships between these independent variables and placental weight. As a consequence, the relationship with the placental to birthweight ratio will be affected, as shown in Tables 10.2 to 10.8. The relationships of the factors to placental weight will be considered below in the variable groupings previously described.
10.4.1 Percentile Related Variables

Birthweight and placental weight both increase as gestational age increases. Considering the ratio, this also increases, as birthweight is increasing at a greater rate than placental weight (Table 10.2). This relationship is not unexpected due to the different growth patterns of the fetus and the placenta during pregnancy, the placenta growing much slower than the fetus in late gestation.68,163

Male placentae are heavier in the same proportion as birthweight and, hence, there is no change in the ratio. The placental size also decreases with decreasing birthweight percentile. This suggests that the placental weight is not reduced in size to quite the same extent as the fetus.

10.4.2 Socio-demographic Variables

As previously shown, single mothers and mothers in de facto relationships were associated with a decrease in birthweight (Table 10.3). There is, however, no indication of any significant change in placental weight, which leads, therefore, to a significant decrease in the ratio.

Similarly, there was no significant change in placental weight associated with maternal education, hence the change in the ratio is due to the decrease in birthweight (Table 10.3).

On the other hand, paternal education showed no change in birthweight, but did show increasing placental weight with lower paternal education (Table 10.3). Hence the decrease in ratio shown on the table is due to the change in placental weight not birthweight as in the case of maternal education.

10.4.3 Maternal Lifestyle Factors

Neither maternal smoking prior to pregnancy, nor smoking during pregnancy showed any statistically significant changes in placental weight (Table 10.4). This is in contrast with the large decreases in birthweight associated with maternal smoking. Thus the changes in the ratio, which increase in magnitude as the number of cigarettes smoked gets higher, seem to be due mainly to the decrease in birthweight.
10.4.4 Genetic Factors

The effects of birthweight, placental weight and the ratio of birthweight to placental weight, in relation to ethnicity is confusing. Whilst birthweight is decreased amongst the Maori and "other" groups, placental weight is not. On the other hand, both birthweight and placental weight are seen to be decreased amongst Asian infants in comparison to Europeans. Pacific Island infants were both heavier and had larger placentae than Europeans (Table 10.4). The ratio shows significant decreases in all categories in comparison to the European category. The change in the Maori, Asian and "other" groups is mainly due to the decrease in birthweight, while that in the Pacific Island group is due to the proportionately greater increase in placental weight than birthweight.

Maternal height which was shown to have an effect on birthweight, also shows a similar effect on placental weight, hence there is no noticeable change in the ratio.

10.4.5 Obstetric Factors

The changes in birthweight and placental weight due to antenatal related variables are somewhat mixed (Table 10.5). Whilst there was a decrease in birthweight seen with; more ultrasounds, number of admissions to the antenatal ward, and days spent in the antenatal ward, there was no significant decrease in placental weight. The changes in the ratio were also non-significant.

The number of antenatal visits showed no change in placental weight and whilst there were small decreases in birthweight, the changes in the ratio were non-significant.

When maternal age is considered, birthweight decreases with decreasing maternal age, but there is no change in placental weight (Table 10.6). Hence the ratio decreases with maternal age as a consequence of decreasing birthweight. There was no statistically significant change in placental weight associated with either of the maternal blood pressure variables, however, the magnitude of the point estimates for these changes in placental weight were large enough to neutralise the effect of the decreased birthweight on the ratio. Maternal haemoglobin showed no effect on birthweight. However, mothers with low haemoglobin levels had significantly larger placentae. This accounts for the decreased ratio for mothers with the lowest haemoglobin levels.
As for birthweight, increasing placental weight was seen with increasing parity, hence the negligible changes in the ratio (Table 10.7). Also, there are no significant differences in placental weight due to either previous miscarriages or induced abortions, hence no effect on the ratio. A previous low birthweight infant was associated with a smaller placenta, again neutralising the effect of the decrease in birthweight on the ratio. The change in the ratio due to a previous perinatal death was due to an increase in placental weight whilst there was no change in birthweight. A previous caesarean section was seen to increase placental weight as well as birthweight. The increase in birthweight was proportionately larger, hence, a significant decrease in the ratio.

10.4.6 Nutritional Factors

As for birthweight, placental weight was seen to decrease when maternal weight gain during pregnancy was low (Table 10.8). Hence the ratio shows no significant change. The mother working part-time was associated with a decrease in both birthweight and placental weight. The decrease in placental weight was proportionately larger, however, and, hence, there was also a significant increase in the ratio. On the other hand, for mothers who worked full-time, placental weight was decreased while there was no change in birthweight, hence the increase in the ratio for this group.

10.4.7 Summary

The relationships described above seem to fall into three general categories:

i) The relationship between the variable of interest with birthweight and placental weight changes both birthweight and placental weight in similar proportions. Hence there is no change in the ratio with the independent variable. Variables that change in this manner include: infant sex, parity, and number of miscarriages.

ii) Birthweight changes in relation to the independent variable in a greater proportion than placental weight changes, or birthweight changes and placental weight does not. This has the effect of decreasing the ratio if birthweight is decreased, or increasing it if birthweight is increased.

This case seem to apply to the majority of the variables including gestation. Other variables that show a greater proportional decrease in birthweight than placental weight are; a previous caesarean section,
admission to the antenatal ward, ethnicity, maternal height, and smoking during pregnancy. Variables that show a decrease in birthweight and no change in placental weight are: maternal age, maternal education level, marital status, the number of antenatal visits, and smoking prior to pregnancy.

Of these variables the one of most interest and possibly of most importance is that of smoking. The effect of smoking on birthweight has previously been shown to be greater during pregnancy than before pregnancy (Chapter 7). This also seems to be the case in relation to placental weight. However the changes are not as large as one may have suspected and are smaller in size than those of birthweight. There do not seem to be any straightforward explanations for the effects of any of the other variables.

iii) The independent variable changes placental weight in a greater proportion than birthweight or changes the placental weight but not birthweight (which is the opposite to situation ii).

Variables for which the placenta is affected greatest are: work in pregnancy, blood pressure after 20 weeks, and maternal haemoglobin.
Chapter 11: Discussion

11.1 Definition of Percentile Curves and Small for Gestational Age

To use SGA as an outcome it is essential to have accurate percentile curves that are appropriate for the population of interest. Therefore, the factors for which percentile curves are defined are most important.

The most important factor in relation to birthweight is gestation, as birthweight increases with increasing gestational age. Hence percentile curves must be specific for gestational age.

There is little doubt that gestational age specific curves must be specific for sex as female infants are lighter than male infants. More complex issues have been discussed in chapter 2 and are summarised below.

As mentioned in chapter 2, some ethnic groups seem to show an increased risk of giving birth to smaller infants than others. This increased risk is mainly due to other factors associated with ethnicity, more specifically those of a socio-economic nature, maternal size, and smoking. These are known to differ amongst ethnic groups in New Zealand. Another problem which makes production of ethnic specific curves difficult in New Zealand is the small number of births each year within ethnic groups.

Another issue comes from the movement of ethnic populations around the world. An example of this is the difference in birthweights amongst second generation Chinese in America, who are more like Americans than Chinese. This has tended to be less of a problem in New Zealand. Pacific Islanders are a major immigrant group, and have heavier infants. However, more recently there have been larger numbers of immigrants coming from Asia and it will only be a matter of time to see whether second generation Asians show the same patterns as have been observed in countries like the United States.

Parity is an issue since primiparous mothers give birth to lighter infants than those who have previously given birth. For this reason it would seem reasonable to have separate percentile curves for primiparous and multiparous mothers. However, it is uncertain whether mothers who have had a previous spontaneous or induced abortion should be considered to be primiparous or multiparous.

Adjustment for maternal height, and to a lesser extent maternal weight, has been to the fore recently in discussing birthweight. This adjustment is plausible in that maternal height especially may affect the
genetic potential of a fetus. However, it is uncertain whether an infant that is small, partly due to constraint of maternal size, is better or worse off than an infant of the same birthweight from a mother who is larger.

The effect of producing percentile curves that are specific for a number of factors has the same effect as in a case-control study where subjects are matched on a number of factors. The purpose is to remove confounding of the variables for which they are matched. In fact, matching can introduce confounding with the variables, since the crude exposure proportion in the controls is distorted in the direction of the cases, so it is advisable to control for these variables in analyses. Producing only sex specific curves as has been done here seems to be the best way to proceed.

Once percentiles have been defined, the next question is how to best define SGA. The different definitions used in different studies make comparison of results difficult. Part of the difficulty in defining a dichotomous outcome from a continuous variable lies in available sample size. An example of this can be seen when the third percentile is used in the analysis of the National Womens Hospital (NWH) dataset (Chapters 7 and 8), resulting in unexpected relationships and unstable models in the multivariate situation (Chapter 8).

It would seem that use of the tenth percentile, where a dichotomous variable is required, will produce a group with a substantial enough size for analyses without containing excessive numbers of infants that are being considered small.

Therefore standardising the definition of SGA as being below the tenth percentile will enable reliable analyses to be carried out and provide studies from which results will be easily compared.

**11.2 Discussion of Appropriateness of Q-Q Plots.**

Whether to use Quantile-Quantile plots to determine where cutoffs should be made, in ordinal or continuous variables, remains contentious. On the one hand, there is the question of whether multiple p-testing is an issue, and, on the other hand, the importance of using appropriate cutoff points.

It has been pointed out that multiple testing invalidates the p-value associated with the chosen cutpoint and that the relative risk associated with a chosen cut point will be biased away from zero.

In contrast, however, are two issues in support of Q-Q plots: firstly, that, in epidemiology, there are few situations of sufficient clarity and knowledge to be able to define *a priori* the single optimal exposure
cutpoint. Arbitrary selection also provides no guarantee of the correct interpretation or pattern of the data. Secondly, probability plots allow one to investigate how risks change with exposure and should be used as a precursor and adjunct to statistical analysis.

The best approach seems to be the use of such plots in conjunction with *a priori* knowledge of how an independent variable is expected to be related to the outcome. This approach is the basis of exploratory data analysis.

No matter how one categorises a variable at the univariate level, there will always be a chance that this may not be the optimal categorisation or even an appropriate categorisation at the multivariate level. It may be appropriate, however, to adjust for multiple comparisons in analyses using methods previously described.

11.3 Discussion of Consistency of Results Between Binary and Continuous Response

Both the binary and continuous outcome situations have advantages and disadvantages which will be discussed below. The main focus on these two different outcome methods in the analyses carried out throughout this thesis has been the consideration of the consistency of the effects of the independent variables.

There are two main concerns when dichotomising a continuous outcome. First is the issue of the loss of information by taking the variable (in this case birthweight) out of its natural form and putting it in a binary form. Second is the question whether the model that is developed using the binary outcome bears a good resemblance to that we would obtain if the all the information of a continuous outcome was used.

Consistency between models using binary and continuous outcomes also requires appropriate groupings of the independent variables whether they be categorical or continuous. Again, the issue of whether an independent continuous variable should be categorised is a topic of much discussion. In the case of independent continuous variables, using them in their continuous form requires knowledge of how they are related to the outcome e.g. is the relationship linear, quadratic etc.

Using a binary outcome and a continuous independent variable makes interpretation of the risks difficult as has been mentioned in Chapter 8 in relation to smoking. Hence, in the binary situation, it is sensible to categorise continuous variables because then the odds ratio has more meaning to the lay person and is more
useful in terms of public health policy. With a continuous outcome it is also necessary to understand how the independent variable is related to the outcome. For the purpose of comparing the risks obtained using a binary outcome and the change in the continuous outcome, it is easier to compare when the independent variable has been categorised in the same way.

Another issue is what a particular risk means for any individual. When a binary outcome is used the risk for a category is the risk for every individual in that category. On the other hand a change in birthweight of 50g due to being in a particular category again is the same for each individual in that category. However this 50g change in birthweight has a much greater proportional effect on, say, a 2000g infant than a 3500g infant.

Comparing the analyses using the binary and continuous outcomes showed relatively consistent models. Any differences in the models using binary and continuous outcomes seemed to be in the variables that were indirectly related to the outcome. Furthermore, the analysis of odds ratios in relation to birthweight changes using both datasets were shown to be reasonably consistent. Each unit increase in the odds ratio equivalent to between 80g and 100g change in birthweight (Fig 6.1, Fig 8.1).

11.4 Discussion of Variables and Relation to Outcomes

The socio-demographic variables in these datasets show relationships at the univariate level that are reasonably consistent between the binary and continuous outcomes.

In the NZCDS dataset, nearly all socio-demographic variables showed a relationship at the univariate level, the exception being the association between socio-economic status and the binary outcome. The variables measuring socio-demography were standard and well tested methods. The use of the Elley-Irving classifications for occupation are, however, reasonably outdated. Marital status is a standard measure used worldwide, however the category for defacto relationships may need to be considered more carefully in future. Education level is difficult to measure due to the diversity of different measures. That of number of years at secondary school may not be the best measure and a system taking into account qualifications may be of more use. However, many people leave school without qualifications and further categorisation within this group may be required.

Marital status and maternal education were the only socio-demographic variables on the NWH dataset and both showed similar relationships to those using equivalent variables in the NZCDS dataset, even though maternal education showed no relationship using the continuous outcome. The reason for this is likely to be
due to the measurement of maternal education in the NWH dataset which was slightly different than that used in the NZCDS dataset.

Socio-demographic variables tend to be confounded by other socio-demographic variables and other variables such as smoking. This is highlighted in the partial model fitted in the NZCDS dataset using the socio-demographic variables where none of the socio-demographic variables showed any statistically significant relationships using the binary outcome, and only marital status showed any relationship using the continuous outcome. This relationship also became non-significant after controlling for other variables.

In the full models the relationships between the outcomes and socio-demographic variables were weak. An atypical pattern was seen between socio-economic status and the binary outcome in the NZCDS dataset. The model suggesting that those in the highest SES group had the highest risk and there being no pattern across the other categories. There was no evidence of this effect using the continuous outcome where birthweight generally decreased with decreasing SES. The NWH dataset showed a similar sized effect of marital status to the NZCDS dataset, but was significant probably due to the greater number of observations in the dataset.

Overall, there seems to be little direct relationship between socio-demographic variables and SGA or birthweight.

Smoking has long been recognised, and still is, the most important factor in relation to birthweight. The size of the effects in well controlled studies tend to be of the order of 2 for smokers in relation to non-smokers, with generally increasing risks with increasing amounts smoked. The only real controversies that exist are those relating to the effects of small amounts of smoking (i.e. 1-4 cigarettes per day), giving up smoking during pregnancy and passive smoking.

This thesis addresses the first two of these issues. The effects of light smokers (i.e. 1-4 cigarettes per day) using the binary outcome were non-significant using the NZCDS dataset in both the univariate and multivariate situations (the odds ratios did however lie between unity and the risk for those who smoked 5-9 cigarettes per day). However, the changes in birthweights were similar to those of the non-smokers in both the univariate and multivariate situations. In general the risks and changes in birthweight were of larger magnitude as the number of cigarettes smoked per day increased, in the NZCDS dataset.
The NWH dataset, however, showed increased risks amongst this group using all three outcomes at the univariate level and these risks continued after controlling for all other variables in the multivariate analysis. The decrease in birthweight for this group was similar to that of those that smoked 5-9 cigarettes per day.

The effects of reducing or quitting smoking in pregnancy are seemingly clear from both the SGA outcome and continuous birthweight outcome point of view, using the NWH dataset. A reduction in smoking reduced the decrease in birthweight, and quitting further reduced the decrease in birthweight. The decrease in birthweight due to smoking seems to be caused mainly by the smoking that occurs during pregnancy.

Lighter smokers are more likely to be able to give up this addictive substance, whilst the heavier smokers are more likely to only be able to reduce the amount smoked. This was the case in the NWH dataset.

The usage of marijuana by pregnant women in New Zealand was previously unknown, and was found to be higher than expected. The use of marijuana is closely related to tobacco smoking and hence is confounded by tobacco smoking. The NZCDS dataset showed an effect of marijuana use at the univariate level, however this was no longer significant after controlling for tobacco smoking. The size of the effect was similar to that reported by previous overseas studies.\textsuperscript{86,100}

It is often quoted that there is no known safe level of alcohol intake during pregnancy. The majority of studies that have looked at alcohol, however, have shown detrimental effects of large amounts of alcohol (usually more than 2 servings per day). Fetal alcohol syndrome is well recognised as a consequence associated with the intake of large quantities of alcohol during pregnancy. The safety of small amounts of alcohol and binge drinking are not as clear. In this thesis, using the NZCDS dataset, small amounts of alcohol do not show any detrimental effects, but, rather, actually show a protective point estimate. The recommendations of total abstinence from alcohol during pregnancy is not supported in this study.

The effects of caffeine are even less clear. One of the problems surrounding these effects is the measurement of caffeine intake. Caffeine is only one of many substances contained within coffee, tea and cola drinks, and different methods of preparing coffee result in large differences of caffeine intake from a single cup. In addition, the amounts of caffeine present in these other drinks are not as high as in coffee, hence most studies focus solely on coffee consumption.

Measurement of caffeine intake is generally fraught with problems. In general, there seems to be little, if any, effect of moderate amounts of caffeine on the fetus. Effects due to large intakes of caffeine have been
suggested. It is likely that these effects are linked with those of smoking and possibly even alcohol intake. Smoking may possibly change the metabolism rate and hence the rate at which caffeine is absorbed.\textsuperscript{173}

The results from the NZCDS dataset, like those of other studies, show no significant effects of caffeine intake using either the binary or continuous outcome. The continuous outcome does suggest, however, a tendency towards a decrease in birthweight with large amounts of caffeine.

The main debate regarding genetic potential must centre around whether the infant of a small mother (which reaches what may be considered to be its genetic potential) is as well off as an infant of a larger mother that does not reach its genetic potential, yet may still be larger.

The effect of ethnicity on birthweight is shrouded in the question of whether it is due to biological, socio-demographic, or cultural factors. Many ethnic minorities are often over represented in the lower socio-economic groups of society and have higher smoking rates. The data from the NZCDS dataset shows no significant difference in risk or in birthweights amongst the ethnic groupings after adjustment for potential confounders. This may in part however be due to the inclusion of anyone not classified as Maori or Pacific Islander as being “other”. The NWH dataset, which was able to divide ethnicity into more categories, showed no differences between those classified as European and those classified as Maori. There was however a significant difference between these two groups and both Asians and Pacific Islanders when birthweight was considered as a continuous variable. As noted in the partial models using the NZCDS dataset, whilst control for maternal size had little effect on the Maori group it had marked effects on the Pacific Island group. Maternal size was unable to be controlled for fully in the NWH dataset due to large amounts of missing data for maternal height, which may account for the large differences seen in Pacific Island and Asian birthweights. Meanwhile, the effect due to Maori ethnicity seems to be most changed by controlling for smoking. Controlling for smoking, however, had little effect on the Pacific Island group. This is not unexpected as Maori have high smoking rates in comparison to the other ethnic groups,\textsuperscript{37,159-161} and the effects of smoking on birthweight are well documented.

The effects of both maternal height and weight seem clear from the analysis of the NZCDS dataset. Women who are smaller either in height or weight have smaller babies, and those who are taller and/or heavier have larger babies. Such influences seem more likely to be related to maternal size than paternal size due to the fact that the fetus grows in the maternal environment. However, additional influences due to paternal size should not be disregarded and need further study.
The effects of maternal size may well be further confounded by nutrition throughout pregnancy. The heavier mothers, who have heavier infants, are more likely to have more ample nutritional stores prior to pregnancy. Furthermore, smaller women may not gain enough weight during pregnancy to allow the fetus to grow to its potential. However, the effect of any given weight gain may be more advantageous to these smaller women than those who already have ample nutritional stores. Due to the possible relationships between maternal height, pre-pregnancy weight, measures of maternal nutrition during pregnancy and maternal weight gain during pregnancy, all these variables should be controlled for where possible.

Obstetric variables are likely to be important as they have a direct effect on the mother and, in turn, an effect on the fetus. Variables such as maternal age and parity, are naturally related to each other. The relationship of some obstetric factors such as maternal age and parity to birthweight are well studied. However, the relationship of some subgroups, such as maternal age in respect to adolescents, are still disputed. Other obstetric factors such as sexual intercourse during pregnancy are less well studied.

The differences in effects of maternal age between the datasets used here highlight these differences. The NZCDS dataset shows a decrease in risk for teenage women using both the binary and continuous outcomes, whilst the NWH dataset (using slightly different categories) shows an increased risk using the model for between the 3rd and 10th percentile, and a decrease (though not statistically significant) using birthweight continuously. The model for below the 3rd percentile suggested a decreased risk for the younger women as did the NZCDS dataset.

The effects of parity previously noted were confirmed in this thesis, with first born infants being significantly smaller than subsequent infants. The data here also suggests increasing infant size with subsequent pregnancies. As stated previously the major issue relating to parity remains that of whether pregnancies that are not carried to delivery, either through abortion or miscarriage, carry forward to subsequent pregnancies the effects that take place when an infant is successfully carried to birth. The chances of these benefits being carried by pregnancies that do not end in a live birth could well be related to the length of gestation the fetus is carried for. The data contained in this thesis generally shows no effect of previous miscarriages or induced abortions. This suggests that they may well not be carried for long enough to have any of the beneficial effects mentioned above.

Connected with such issues is the effect of having previously had a small infant. Those women that have had a previous small infant seem more likely to have another one, even with the supposed benefits of the previous
pregnancy. These effects may be due to other predisposing factors that are common to both the pregnancies, for example maternal height, and smoking.\textsuperscript{191}

As expected twin pregnancies were at an increased risk of being small and the risk was more increased for the second born twin. This effect is well documented. However the cause of this effect, possibly related to the placenta and the way in which the cord is attached to the placenta needs further research. Urinary tract and genital tract infections seem to show little relationship to birthweight directly, although they have been reported to effect gestation.

Late antenatal care seems to increase the risk of a small baby. Late antenatal care is related to socio-economic factors. However, the effect on birthweight continues after control for socio-economic factors in the NZCDS dataset. Antenatal care is an area that requires careful consideration. The early attendance at antenatal classes or clinics may well be able to alleviate some of the problems associated with an at risk pregnancy. Such benefits may, however, be likely to be lost not only on women who are late attenders, but also women who have had previous children and feel that antenatal care is not necessary. In the NWH dataset, the univariate analyses suggested decreased birthweights for mothers admitted to the antenatal ward although these effects did not remain significant after controlling for other factors. This may suggest that mothers with antenatal problems are being identified and the effect on birthweight alleviated.

A summary of important variables and those that showed a significant relationship in multivariate analyses using the NZCDS and NWH datasets is provided in the following table. In general the results using both datasets are consistent, as are those using the binary and continuous outcomes.
Table of important variables and variables relationships to birthweight in respect to binary and continuous outcomes using the NZCDS and NWH datasets

<table>
<thead>
<tr>
<th></th>
<th>NZCDS Binary</th>
<th>NZCDS Continuous</th>
<th>NWH Binary</th>
<th>NWH Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Education</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Maternal social support</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Marijuana use</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine consumption</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Maternal height</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Maternal pre-pregnancy weight</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Parity</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Previous miscarriages</td>
<td></td>
<td></td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Previous low birthweight infant</td>
<td></td>
<td></td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Antenatal care</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple birth</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Maternal weight gain in pregnancy</td>
<td></td>
<td></td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

N: No significant relationship found
Y: Significant relationship found
11.5 Placental Relations

The work associating birth measurements and disease status in adult life is relatively new. The notable feature of the analysis in chapter 10 relates to the way birthweight and placental weight change, both individually and in relation to each other. As birthweight decreases or placental weight increases the ratio of birthweight to placental weight decreases and vice versa.

The questions that need to be addressed are what factors affect placental weight and how these changes affect the birthweight to placental weight ratio. The question of how the changes in placental weight or the birthweight to placental weight ratio are related to outcomes in childhood and adult life remain unanswered.

In the context of disease in adult life and the relation of these variables, is placental weight the important factor or is the birthweight to placental weight ratio the important factor?

Some of the relationships with placental weight, such as the relationship with gestation where placental weight increased with increasing gestation are expected. A number of others, such as the association between maternal haemoglobin and placental weight, where placental weight increases with decreased maternal haemoglobin, have been reported recently by others. The effect shown here by maternal work is also consistent with work recently published which showed that regular recreational exercise increases the growth of placental volume in the mid-trimester of pregnancy.

Unexpected relationships with placental weight have also been shown in this thesis. The one that stands out most is that of smoking. Smoking is known to increase the risk of having a small infant and significantly decreases birthweight. The evidence here suggests, however, that smoking does not alter placental weight at all. This brings into question how such an effect takes place.

The real issue relating to disease in later life may revolve around whether the change in placental weight is important or whether a change in the birthweight to placental weight ratio is important. The ratio can be changed by either a change in birthweight alone, e.g. smoking (Table 10.4), or in placental weight alone e.g. haemoglobin (Table 10.6), or by a greater proportional change in birthweight or placental weight to each other. The data in this thesis shows that placental weight and birthweight often change in proportion with each other and, hence, produce no change in the ratio, e.g. parity (Table 10.7).
Another area of great interest is the relationship of twins and the placenta. This also is brought to the fore by the analysis in chapter 9. Twins often have fused placentae and the proportion of the placenta belonging to each twin can be difficult to determine. The "transfusion effect" is well documented and is seen to be the cause in many situations of one twin being larger than the other. Techniques are now becoming more common which allow surgical procedures to be carried out on the placenta to alleviate this effect, which otherwise can result in the loss of one fetus often also leading to the loss of the other.

11.6 Future Research Directions

A number of factors are known to be associated with birthweight, some of these have shown consistent results throughout the world, especially the effect due to maternal smoking. A number of other related factors have unclear pathways, such as the effects of maternal weight gain.

Maternal nutrition both prior to and during pregnancy is being recognised more and more as a factor that effects the growth of the fetus, though the size and timing of these effects are still unclear. Maternal nutrition clearly depends on ready stores prior to pregnancy and those gained during pregnancy, both of which are modifiable, in the case of planned pregnancies.

Nutrition has many components; caloric intake, protein, vitamins, and minerals amongst many others. Deficiency of any of these in pregnancy may have the ability to produce an effect on fetal growth.

Another factor on which even less knowledge is known is the effect of exercise during pregnancy. This relates to both maternal leisure exercise and exercise resulting from work. Maternal exercise is, by definition, likely to be related to maternal nutrition, as exercise uses at least some of the energy gained from nutritional intake, which therefore becomes unavailable for use by the developing fetus.

The relationships between birth measurements and disease in adult life are far from understood. The analysis reported in chapter 10 has shown different relationships between independent factors and both placental weight and birthweight. In relation to disease in adult life, the important factor could be related to either placental weight or the birthweight:placental weight ratio. This area of work is still recent and further investigations are needed for the understanding of relationships between independent factors and these two outcomes. Furthermore, the effect on birthweight of factors such as maternal nutrition and exercise are also likely to show relationships with placental function and may help in developing an understanding of how events during pregnancy can effect later life.
As far as placental function is concerned, placental pathology may also have a large part to play in helping to determine how communication takes place between the placenta and the fetus and why some substances may be transferred across the placenta to the fetus while others are inhibited. Another, frequently overlooked, point here may be the relationship with the umbilical cord, the length of the cord, and how it is attached to the placenta.

11.7 Conclusions

This thesis has shown that in New Zealand relationships to birthweight are similar to those overseas. The most important factor, as in other developed countries, is that of maternal smoking, especially during pregnancy. The size of the risks and changes in birthweight have also been shown to be consistent with those found in the international literature.

The public health implications of this thesis mainly relate to maternal smoking, which has been shown to be associated with large decreases in birthweight, the magnitude of such decreases increasing with the amount smoked. Public health policy clearly needs to strongly deter pregnant women from smoking.

11.8 Final Overview

This thesis has made a number of advances in the understanding of small for gestational age, especially in New Zealand. Of note are the following:

1) The production of New Zealand sex specific percentile curves for birthweight, which are being used in a number of hospitals.

2) The risk factors in New Zealand are much as they are in the rest of the world and smoking has been confirmed as the major risk factor for SGA infants in New Zealand. Furthermore, these risk factors continue to show significance in these dataset after controlling for a number of variables in multivariate analyses. This also helps to expand international knowledge as few studies are able to control for a large number of confounding variables.
3) Of particular interest are the effects described in relation to smoking, both prior to and during pregnancy and the effects of both reducing the amount smoked and quitting smoking. These findings are relatively new and may well be important in the determination of public health messages regarding smoking during pregnancy.

4) The analysis of variables using both a priori and Quantile-Quantile plots, has shown that the categorisations generally agree.

5) Relationships between the binary outcome of SGA and the continuous outcome of birthweight were consistent. Furthermore the results between the two datasets (NZCDS and NWH) were also consistent making the results more generalisable.

6) The relationships between factors and their different influences on birthweight and placental weight have not been reported previously. The reasons and meanings of these findings however remains unclear.

The thesis does however have limitations:

1) Neither of the datasets were collected specifically to look at SGA. However, both datasets are expected to be relatively free of biases and provide a good picture of the associations between the factors studied and the outcome.

2) Nutrition and exercise in pregnancy are obviously important factors in relation to birthweight. These datasets, unfortunately, did not have any measure of these and hence this thesis was unable to control for them.

3) Unfortunately the birthweight percentile curves are not being used in all hospitals in New Zealand due to the limitation of not having head-circumference and crown-heel length percentiles from the same data.
Bibliography


Appendix A: Programs to Create Q-Q Plots

Program 1

libname library 'c:\home\library';
goptions device=win cback=white colorn=black;

data temp;
merge sue.sgaprem
  cards.cardh (rename=(hidh=id));
by id;
if baby=2 then sga=1; else if baby=3 then sga=2;
run;

data a;
set temp; /* set to appropriate dataset */
keep sga h100;
if sga=1; /* set to appropriate outcome variable */
if h100>=0;
run;

proc sort data=a;by h100;run;

data b;
set temp;
keep sga h100;
if sga=2;
if h100>=0;
run;

proc sort data=b;by h100;run;

data temp2;
array ct{10};
set a; file print;
do i=1 to 10; /* loop through appropriate categories adding number */
if h100<=i-1 then ct(i)+1; end;
run;

data temp3;
array dt{10};
set b; file print;
do i=1 to 10;
if h100<=i-1 then dt(i)+1; end;
run;
Program 2

data c;set temp2;if _n_ =142;run; /* Get last observation */
data d;set temp3;if _n_ =1361;run;

data c;
set c;
array ct{10};array newct{10};
do i=1 to 10; /* loop through number of categories */
newct{i}=ct{i}/142; /* divide arrays by numbers in each group to get appropriate proportions */
end;
run;

data d;
set d;
array dt{10};array newdt{10};
do i=1 to 10;
newdt{i}=dt{i}/1361;
end;
run;
Program 3

/* Need to run d:\sas\sasmacro\annomac.sas before this program will run */

filename testing 'c:\testing.asc';
data e;set c;file testing;put newctl--newctl0;run; /*appropriate vars */
data e; infile testing;input p @@;run;
data f;set d;file testing;put newdt1--newdt10;run;
data f; infile testing;input q @@;run;
data pq;merge e f;run;

title 'QQ-plot for SGA - variable '; proc print;run;

data g;
do or=1 to 3 by 0.5; do d=0 to 1 by 0.01;
  c=1-d; b=d/((c*or)+d); a=1-b; output; end;
end;
run;
data i; set pq g; run;

goption device=vga;
symbol1 v=" i=join; symbol2 v=" i=join; symbol3 v='+' i=join l=2;
axis1 length=9.6 CM; /* Change to 18cm for printing */

proc gplot data=i;
plot a*c b*d p*q/overlay haxis=axis1 vaxis=axis1;
run;
goptions device=hpljs3 horigin=2.0cm vorigin=1.5cm hsize=17.5cm vsize=26.7cm;

title f=swissl j=c h=3 'Fig 5.11 Q-Q plot for Antenatal care';

symbol1 v="i=join;symbol2 v="i=join; symbol3 v=’dot’ i=join l=1 w=5;

data anno;
xsys=’2’;yysys=’2’;
%label(0.22410,0.14085,’1’,*,0,0,1,swissl,2)
%label(0.63777,0.49296,’2’,*,0,0,1,swissl,9)
%label(0.84864,0.72535,’3’,*,0,0,1,swissl,2)
when=’a’;
run;

axis1 value=(f=swissl h=0.4cm)
        length=15 CM /* Change to 16cm for printing */
        order=0 to 1 by 0.1
        minor=none
        label=(h=0.5cm a=90 j=c f=swissl 'Proportion of Cases');
axis2 value=(f=swissl h=0.4cm)
        length=15 CM
        order=0 to 1 by 0.1
        minor=none
        label=(h=0.5cm j=c f=swissl 'Proportion of Controls');

proc gplot data=i;
plot a*c b*d p*q/overlay vaxis=axis1 haxis=axis2 annotate=anno;
run;
proc gplot data=i;
plot a*c b*d p*q/overlay vaxis=axis1 haxis=axis2 annotate=anno;
run;
Appendix B: Example of SAS Program for Logistic Regression

/* Run chp5anal.sas first to set up dummy variables */

/* Start with everything in the model */

proc logistic data=temp nosimple;
model sga=agefsch1 agefsch2 occup2 occup3 married mssic agebth1 agebth2 agebth3 prevpg0 prevpg1 prevpg2 antinat uti maori pi ht1 ht3 wt1 wt3 smok2 smok3 smok4 marijuna nmdrwkf2 nmdrwkf3 gramft2 gramft3;
run;
Appendix C: Example of SAS Program for Linear Regression

/* Now to run the models with a continuous outcome */

proc reg data=temp;
model bwt=agefsch1 agefsch2 occup2 occup3 married mssic agebth1 agebth2 agebth3 prevpg0 prevpg1 prevpg2 antinat uti maori pi ht1 ht3 wt1 wt3 smok2 smok3 smok4 marijuna nmdrwkt2 nmdrwkt3 gramft2 gramft3;
run;
Appendix D: Example Program of Standardisation and Cluster Analysis

options ls=80 ps=500;

symbol1 v=star c=blue;
symbol2 v=diamond c=red;
symbol3 v=plus c=green;
symbol4 v=+ c=cyan;

proc standard data=temp mean=0 std=1 out=stand;
var v114 v115;
run;

proc fastclus data=stand out=clust1 maxc=2;
var v114 v115;
run;

proc freq data=clust1;
table cluster;
run;

title1 f=swiss j=c h=1.5cm 'Fig 9.6 Euclidean distances with 2 clusters';

proc gplot data=clust1;
plot q115*q114=cluster /vaxis=axis1 haxis=axis2 nolegend;
run;

proc fastclus data=stand out=clust1 maxc=3;
var v114 v115;
run;

proc freq data=clust1;
table cluster;
run;

title1 f=swiss j=c h=1.5cm 'Fig 9.7 Euclidean distances with 3 clusters';

proc gplot data=clust1;
plot q115*q114=cluster /vaxis=axis1 haxis=axis2 nolegend;
run;